Chapter 11

HUMAN PHYSIOLOGICAL RESPONSES TO COLD STRESS AND HYPOTHERMIA

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INTRODUCTION

Conducting military training or combat missions in cold environments poses a dual challenge: protecting the personnel from hypothermia and other forms of cold injury while also realizing the objectives of the mission. The goals of this chapter are to describe the components of the thermoregulatory system that influence peripheral and core temperature in cold environments, how the components respond to a cold environment, and what subsequently occurs when they are unable to maintain core temperature. In this chapter, we discuss the workings of the thermoregulatory system and emphasize the effects of hypothermia from the perspective of field medical practice.

Three major categories of hypothermia are recognized, based on the environment in which the hypothermia occurs (eg, air, water, high altitude), and on the physiological status of the threatened individual. Regardless of its origin, hypothermia is defined as a 2°C decrease in core temperature.[1] Normal core temperature is usually considered to be 37°C for brain, heart, and lungs. Although the clinically defined value for hypothermia is 35°C, this must be considered a rough estimate. Some subjects who experience a rapid decrease in core temperature might have a 36°C core temperature and demonstrate signs of hypothermia that are usually associated with a much lower core temperature. Regardless of the precise core temperature, hypothermia eventually causes a decrease in metabolic rate; this may allow the entire body to survive very cold temperatures and hypoxic states, and be rewarmed without any long-lasting debilitation. The coldest core temperature from which a person has been successfully rewarmed is 15°C.[2] From a military perspective, hypothermia will cause a decrease in overall effectiveness of the casualty, but, paradoxically, the decreased metabolic rate will allow for a much greater time in which the casualty can be rescued.

Hypothermia is classified as primary, secondary, and clinically induced (iatrogenic).[3] *Primary* hypothermia refers to the condition in which the casualty has normal thermal regulatory responses, but these are ineffective against the environment (Figure 11-1). This condition may be seen in any cold weather training scenario (eg, US Navy SEALs undergoing cold water exercises). Although the participants are physically fit, the cold environment will eventually overwhelm their physiological defenses and they will develop hypothermia.

Secondary hypothermia is caused by impaired thermoregulation, the result of an altered physiological state that may be caused by illness, fatigue, or injury. Impaired thermoregulation causes a disproportionately greater effect on the casualty's ability to tolerate cold (ie, cold environments will induce a decrease in core temperature). Secondary hypothermia may explain many of the cold weather casualties in previous wars. In these situations, the troops were fatigued and had insufficient food, clothing, and fluid. Consequently, the cold environment overcame their physiological responses, and hypothermia ensued. For example, Hannibal, Napoleon, and Hitler all experienced major losses during campaigns in cold weather; a majority of their cold-induced losses probably had secondary hypothermia. An injured, fatigued, or sick soldier in a cold environment can easily develop secondary hypothermia. A soldier who has lost blood and is dehydrated will not be able to respond adequately to the temperature challenges of a cold environment. Any environment that is cooler than the body will promote body cooling (even 70°F or 80°F). Thus, hypothermia can occur in deserts or jungles if an individual is dehydrated, fatigued, or injured. The time for the onset of hypothermia depends on a large number of factors: clothing, body size, metabolic rate, physiological state, hydration, and nutritional status. In military situations, the onset of hypothermia is insidious. It occurs gradually and poses a major threat for completion of military operations.

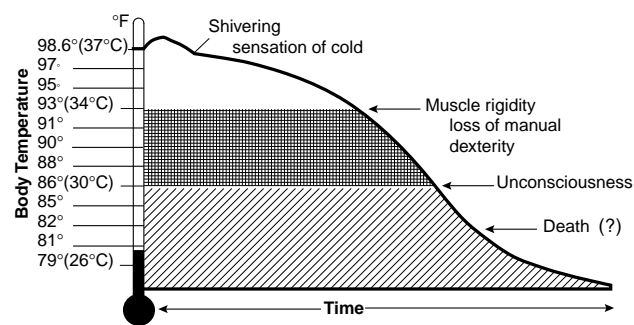*Clinically induced* hypothermia, on the other

Fig. 11-1. Core temperature decrease leading to hypothermia. The diagram demonstrates the schematic representation of the fall of core temperature with both primary and secondary hypothermia. The question mark by the term "death" refers to the life-sparing property of hypothermia—in certain conditions.

EXHIBIT 11-1

HYPOTHERMIA-INDUCING ENVIRONMENTAL AND PATHOLOGICAL CONDITIONS

Increased Heat Loss

　Environmental
　　*Immersion
　　*Nonimmersion

　Induced Vasodilation
　　*Pharmacological
　　*Toxicological

　Erythrodermas
　　*Burns
　　Exfoliative dermatitis
　　Ichthyosis
　　Psoriasis
　　Iatrogenic factors
　　　Cold infusions
　　　Emergency childbirth
　　　Heatstroke treatment

Decreased Heat Production

　Endocrinological Failure
　　Diabetic and alcoholic ketoacidosis
　　Hypoadrenalism
　　Hypopituitarism
　　Hypothyroidism
　　Lactic acidosis

　Insufficient Fuel
　　*Extreme physical exertion
　　*Hypoglycemia
　　*Malnutrition
　　Kwashiorkor
　　Marasmus

　Neuromuscular Physical Exertion
　　Lack of adaptation
　　Extremes of age
　　Impaired shivering
　　Inactivity

Impaired Thermoregulation

　Peripheral Failure
　　Neuropathies
　　*Acute spinal cord transection
　　Diabetes

Central Neurological Failure
　　Cardiovascular accident
　　*Central nervous system trauma
　　Metabolic cause
　　Toxicological cause
　　Pharmacological cause
　　Anorexia nervosa
　　Cerebellar lesion
　　Congenital intracranial anomalies
　　Hyperkalemic periodic paralysis
　　Hypothalamic dysfunction
　　Multiple sclerosis
　　Neoplasm
　　Parkinsonism
　　Subarachnoid hemorrhage

Miscellaneous Associated Clinical States
　　*Multisystem trauma
　　*Recurrent hypothermia
　　*Episodic hypothermia
　　*Infections (bacterial, viral, parasitic)
　　Carcinomatosis
　　Cardiopulmonary disease
　　Giant cell arteritis
　　Hodgkin's disease
　　Paget's disease
　　Pancreatitis
　　Sarcoidosis
　　Shaken baby syndrome
　　Shock
　　Sickle-cell anemia
　　Sudden infant death syndrome
　　Systemic lupus erythematosus
　　Uremia
　　Vascular insufficiency
　　Wernicke-Korsakoff syndrome

*Major cold weather challenges to military operations
Adapted with permission from Danzl D, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies.* 3rd ed. St Louis, Mo: Mosby–Year Book, Inc; 1995: 59.

hand, is defined as a decrease in core temperature that is induced for various surgical procedures such as coronary bypass. This chapter will not further discuss iatrogenic hypothermia but instead will emphasize primary and secondary hypothermia as it relates to military operations.

Because various environments and physiological conditions influence the development of hypothermia and the effectiveness of rewarming, there are various etiological factors for secondary hypothermia that are more commonly associated with military operations (eg, extreme physical exertion, multisystem trauma). Others are more frequently found in military rescue operations, in which American troops rescue civilians, particularly those at the extremes of age, who are in extreme hostile environments and are suffering from conditions such as dehydration and malnutrition (Exhibit 11-1).

Owing to the lessons of history, most modern military forces have adopted various measures to counter the development of hypothermia. Much of their research has focused on various clothing and energy-rich diets. Other research studies have been conducted to understand the interplay of the various components of the thermoregulatory system: the peripheral receptors, which communicate with the brain via the spinal cord; and the cardiovascular, respiratory, renal, circulatory, gastrointestinal, endocrine, and immune systems. One of the goals of this kind of research is to develop a "predictive model" that will help predict the onset of hypoth-

ermia, and more importantly, when a decrement in performance, or even death, will occur. Such a task is daunting because the model must include the physical factors that determine heat transfer as well as the effects of sleep deprivation, dehydration, the lack of food, and the like. Some of the challenges that are yet to be addressed by the model are the effects of psychological underpreparedness in a cold environment as well as any major gender differences. Studies by Hodgdon and colleagues[4] suggest that if a person is adequately prepared (eg, proper clothing, well hydrated, etc), then cold stress leading to hypothermia will not occur. Models are only validated to core temperatures that relate to mild hypothermia and as such cannot predict death with any scientific precision. It is ethically impossible to conduct such experiments. Thus, modeling is important but it cannot be a valid predictor of various stages of hypothermia.

In modern times, as in previous battle campaigns, hypothermia in military training or combat operations is not due to the underpreparedness of the operations but rather to unforeseen situations. During the Falkland War, the British suffered many cold-associated injuries because their timetable for capturing various strategic positions was completely altered, owing to the effectiveness of Argentine sharpshooters. The sharpshooters kept many British soldiers in very cold environmental conditions for much longer than the 1 hour that the timetable had called for.[5]

CORE AND PERIPHERAL TEMPERATURES

The best method to assess the degree of hypothermia and initiate appropriate medical intervention is by measuring the core temperature. Unfortunately, the technologies are not yet available for accurate measurements in the field. In most cases, the core temperature is controlled relative to the changes in peripheral temperature. Peripheral and core thermal receptors send important information to the central nervous system, which mediates all the cold-induced psychological and physiological responses.

Core Temperature Measurements

The measurement of core body temperature is necessary to assist the medical officer in the care and management of the hypothermic casualty, as well as to be the critical measurement in various scientific studies (eg, effectiveness of rewarming methods or different protective suits). In battlefield situations, measuring core temperatures is not prac-

tical. However, because the results of laboratory human studies are used to persuade military commands to make various decisions (eg, to purchase one form of heating systems or another), it is important that accuracy of the different core temperature monitoring systems be presented. Also, in the event that advances in technology allow for the monitoring of core temperatures in the field, the strengths and weaknesses of various anatomical sites to accurately reflect core temperature need to be recognized. Unfortunately, skin temperature cannot be used as a surrogate for core temperature. The sites that have been commonly used are oral, rectal, axillary, tympanic, and esophageal. The advent of easy-to-use tympanic temperature devices has sparked their widespread use for measuring core temperature. In thermally stressful environments, however, the tympanic temperature is not an adequate reflection of core temperature.[6] In a recent study, three different infrared detectors were com-

pared against esophageal temperature in subjects who were made hypothermic by cold water immersion. The temperatures registered by the three different infrared devices were 1.06°C lower than the other core values in subjects whose hypothermia ranged from 36.5°C to 33.3°C. The major reason for this discrepancy is that in all three devices, the cone of the infrared detector was too large to get an accurate reading of the tympanic membrane.[7]

Besides the technical problem, the tympanic temperature is influenced directly by the temperature of the venous blood of the face and indirectly by the temperature of the environment surrounding the head. In any situation in which the skin temperature of the face is being altered by the environment, the tympanic temperature reading will be false with respect to the core temperature.[8] Livingstone and colleagues[9] were able to show that cooling the face decreased tympanic temperature. In a defining experiment, McCaffrey and colleagues[10] showed that cooling or heating small areas of the face altered tympanic temperatures. Application of a bag of cold 3°C to 4°C water to an area of the right cheek and orbit results in a fall of tympanic temperature on the right side, while simultaneously, tympanic temperatures rose on the left as a bag of hot (45°C–50°C) water was held against the left cheek. Although the ease of use of tympanic temperature is enticing, its use in field situations is not recommended because environmental influences on the face can render the readings unreliable.

The best measurement of core temperature is taken at the esophagus, but it is extremely difficult to get compliance from subjects (for inserting a small-diameter cable down the nose and throat) at that site.[11] The axilla is not a good site for measuring core temperature because readings are variable, depending on the subcutaneous fat of the subject and the placement of the sensor. Oral temperature may be as accurate as rectal[12] but varying kinds of breathing patterns of subjects, as well as the potential for subjects to bite on the thermometer, preclude its use in the field. For most purposes, the rectal temperature is considered the most practical and accurate measurement; however, it lags behind esophageal temperature.[11] Measuring core temperature by monitoring urinary temperature, as an indirect measurement of urinary bladder temperature, is one way to get a reading on the core temperature of the body in a field situation. Urinary bladder temperature in certain situations closely correlates with pulmonary artery temperature, but in bypass operations it was below nasopharyngeal temperatures.[14]

Peripheral Temperature Sensors

The maintenance and control of core temperature depends on the interplay of two different temperature-sensing systems: the peripheral and the core. The peripheral sensors provide the body its first line of physiological information. Depending on the differences in temperature that the central nervous system (CNS) differentiates between the periphery and the core, various physiological responses will occur (Figure 11-2). Many of the initial responses to a cold environment are triggered by the peripheral thermal receptors of the skin. The sensation of cold is initially triggered by stimulation of specialized nerve endings called cold receptors. When these receptors are activated, they send electrical signals (ie, action potentials) to the brain that are then interpreted as a cold sensation.[15] In addition, these action potentials will trigger various psychological and physiological responses.

There are two groups of cold receptors, superficial and deep, of which approximately 60% are in the periphery. The arrangement of superficial and deep cold receptors suggests that cutaneous cold receptors measure the temperature gradient within the skin.[16] The response of humans to cold sensation is not purely due to the action of cold receptors. Warm and cold receptors have a bell-shaped frequency-to-temperature relationship, and some overlap with each other between the temperatures of 30°C and 40°C.[17] Although both warm and cold receptors have a tonic firing pattern, they respond to their specific stimuli. In other words, a cold receptor will respond to a cold stimulation with a transient excitation and then stay constant, but it can be inhibited by warming. Thus, the practical solution of warming hypothermic victims with warm blankets can mislead both the victim and the medical practitioner. The warm blankets will inhibit the cold receptors from firing, which will lead to a decrease in various physiological responses triggered by the cold, such as vasoconstriction and shivering. Once these responses are abated the rescuers may mistakenly assume that the person is no longer hypothermic. Without measurement of the core temperature, this false impression may lead to the mismanagement of the hypothermic victim.

The cold receptors transmit information on small myelinated fibers at 5 to 15 m/s and on C fibers.[17] There is a constant rate of discharge between 25°C to 33°C. Interestingly, cold receptors also demonstrate a paradoxical discharge between 40°C and 45°C. This discharge is dependent on body temperature. At core temperatures of 37°C and 39°C, the
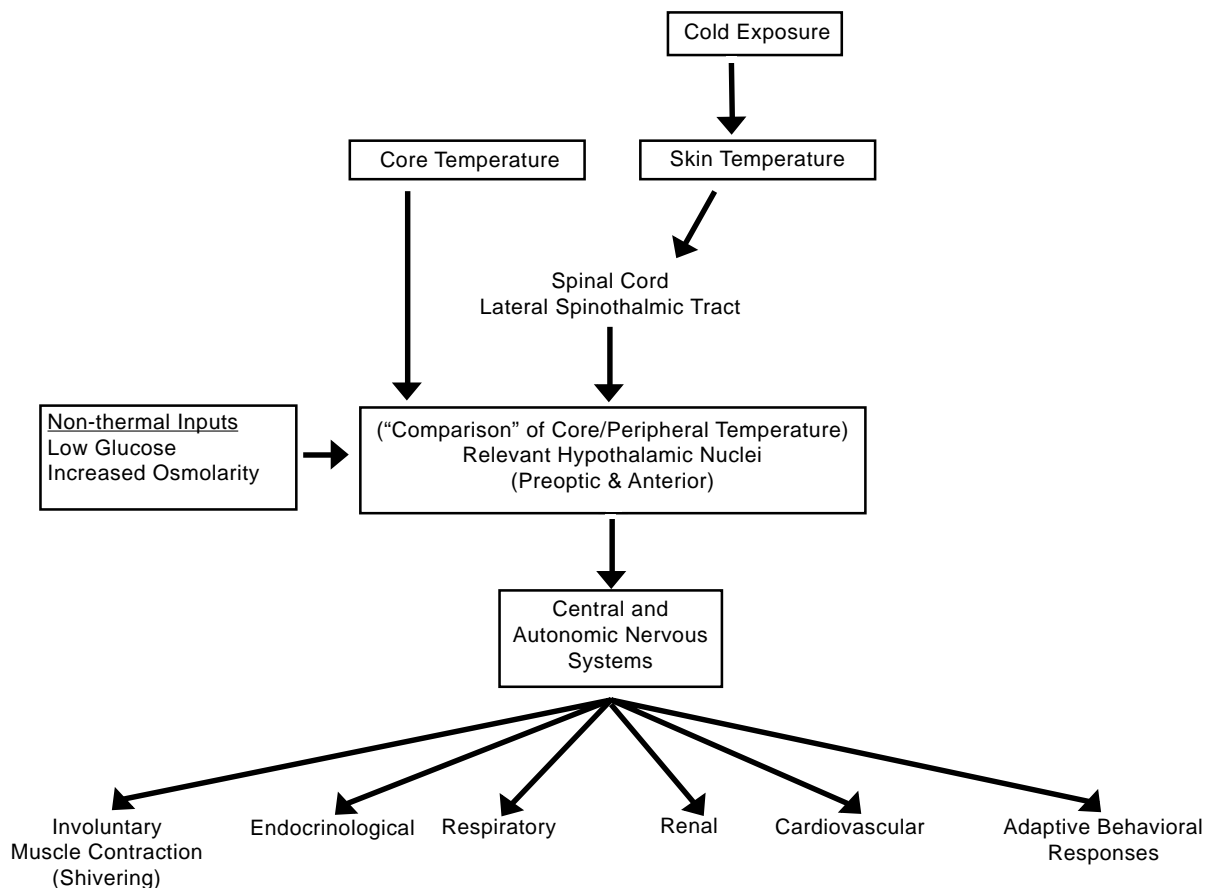
Fig. 11-2. Physiological schemata for thermoregulation in cold environments. The diagram illustrates the roles that peripheral and core temperatures play in driving various coordinated thermoregulatory responses.

cold receptors fire, respectively, at 55°C and 46°C. These data are used to explain the phenomenon of warm stimuli triggering a cold sensation. Once the cold receptor has fired, it rapidly adapts to a new static discharge.[15] Cold receptors, when activated, demonstrate a bursting pattern of doublets or triplets. The interburst interval, burst duration, and number of spikes within a burst all increase monotonically with decreasing temperatures.[16,17] This mechanism might explain how specific information from the cold receptive fields is interpreted in the brain. The mechanism of how the burst frequency is determined can be inferred from a number of studies in which sodium and potassium adenosine triphosphatase activity is inhibited, suggesting that there is an oscillating generator potential at the receptor site that triggers a burst of impulses when a certain threshold is exceeded.[17]

The signals from various afferent fibers enter the spinal cord at two levels: the first, the trigeminal

(the face),[18] and the second, the superficial laminae of the dorsal horn (the rest of the body).[19] Where do these signals eventually terminate? The signals do not seem to traverse the spinothalamic pathway but probably ascend in the nucleus raphe, and then diverge to the sensory thalamic nuclei and the regulatory hypothalamic areas. Both sets of cold fibers project directly onto the thalamus, where the signals are initially interpreted.[20,21] (Interestingly, we are not able to accurately detect our own core temperature. Subjects can sense that they are getting cold, but there is no correlation between core temperature and perception of cold temperature.)

Certain descending pathways from the brain also influence the ascending signals from the cold receptors.[18,19] This area is not yet well studied. These descending pathways may be the key to our understanding of why certain individuals are not bothered by cold environments, because these descending pathways may influence the firing of the cold receptors.

THERMOREGULATION: THE BRAIN

The body's reaction to cold stress is controlled by the CNS, which can be likened to a central computer that controls all physiological systems. However, the brain itself can be cooled, which affects its own viability as well as its ability to control the various systems in terms of thermoregulation. The effects that cold environments have on the brain are multiple, but the area with the greatest interest deals with the hypoxic sparing effect that cold temperature has on brain function. The areas of brain thermoregulation covered in this chapter that compromise military operations are those dealing with motor control and circadian rhythms and sleep.

Hypothalamus

The incoming signals from the skin and visceral afferents will influence the hypothalamus (a major thermoregulatory control site), which will then trigger various thermoregulatory physiological responses. In engineering terms, certain parts of the hypothalamus are considered to be the thermostat of the body and will either increase or decrease core temperature by triggering behavioral and physiological responses. Also, the hypothalamus itself responds to temperature changes in the brain. When the temperature in the rostral part of the hypothalamus is changed, several thermoregulatory responses can be evoked. The preoptic-anterior hypothalamus contains neurons that (1) respond to the temperature in the brain and (2) receive input from the thermoreceptors from the skin and spinal cord.[20,21]

The hypothalamus contains three kinds of neurons: cold-sensitive, warm-sensitive, and temperature-insensitive. The thermosensitive neurons will increase their firing if the temperature changes.[22] All the responses that occur with the initial exposure to cold or a drop in core temperature, or both, are in many ways dictated by the hypothalamus and other CNS sites. That is to say, the hypothalamus is not the singular site that controls the thermoresponse to cold, because the spinal cord has been shown to be another site.[23,24]

The system is even more sensitively programmed, in that certain neurons in the hypothalamus

HEAT PRODUCTION

| Exercise or Shivering |
| Unconscious Tensing of Muscle |
| Higher Basal Rate |
| Fever |
| Special Dynamic Action of Food |
| Basal Heat Production |

| Carb | Fat | Prot |

HEAT LOSS

| Sweating & Panting |
| ↑ Blood Flow to the Skin |
| Change in Temperature Gradient |
| Cooler Environment |
| ↓ Clothing |
| ↑ Radiative Surface | ↑ Air Movement |
| Basal Heat Loss |

| Con | Rad | Vap |

Hypothermia   core   Hyperthermia
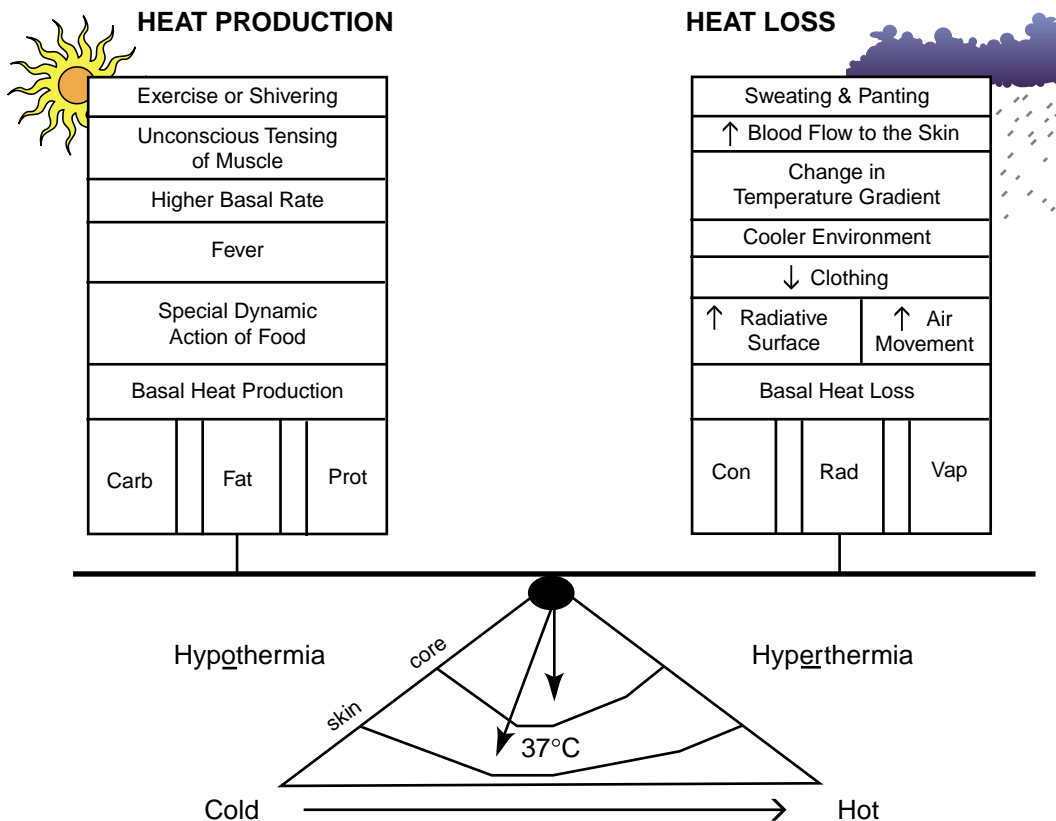
skin   37°C

Cold ⟶ Hot

Fig. 11-3. Balance between heat production and heat loss mechanisms. The drawing illustrates the interaction of skin and core temperatures relative to internal and external factors. Carb: carbohydrates; Prot: proteins; Con: conduction; Rad: radiation; Vap: evaporation.

that respond to cold stimuli also respond to certain chemical changes. For example, when the hypothalamic neurons are exposed to low glucose or increased osmolality,[25,26] the cold-sensitive neurons fire. These nonthermal signals may partially explain the observations, recorded during training operations, of personnel complaining of being cold when they are actually dehydrated or hungry.

When the thermoregulatory system is activated, there will be a number of efferent responses such as an increase in heart rate, peripheral vasoconstriction, tensing of muscles, and higher metabolic rate caused by the release of various hormones. The metabolism is also regulated by the hormones and neural systems that regulate core temperature. The intake of food will also play a major role in maintaining and enhancing the metabolic rate of the hypothermic subject. Figure 11-3 demonstrates the interrelationships between those physiological systems that will produce heat and those environmental and physiological systems that will cause a decrease in heat loss. The diagram demonstrates that skin and core temperatures are independent of each other and that to maintain core temperature requires a balancing act between heat loss and heat production. It also demonstrates the interrelationships among core temperature, skin temperature, and the various physical and physiological factors associated with thermoregulation. This diagram presents a simplistic version of thermoregulation, because the physical processes of conduction and radiation can be used either to heat or to cool subjects.

Cold-induced peripheral vasoconstriction is the first major physiological response to a cold environment. This response is mediated by the autonomic nervous system and elicits the sensation of cold. Vasoconstriction proceeds in a distinct physiological manner, from the tips of the digits to the central part of the hand (Figure 11-4). Over 4 minutes, the tips of the fingers become more vasoconstricted and, therefore, cold, until eventually even the palm is cold. The exquisite control of the autonomic nervous system in controlling blood flow is shown in Figure 11-5, in which one hand has just been removed from a glove, whereas the other has been in a cold room. Notice also that the face is cool except for the forehead and area adjacent to the nose. The same phenomenon occurs in the feet (Figure 11-6) and the rest of the body. Many physiological and pharmacologi-
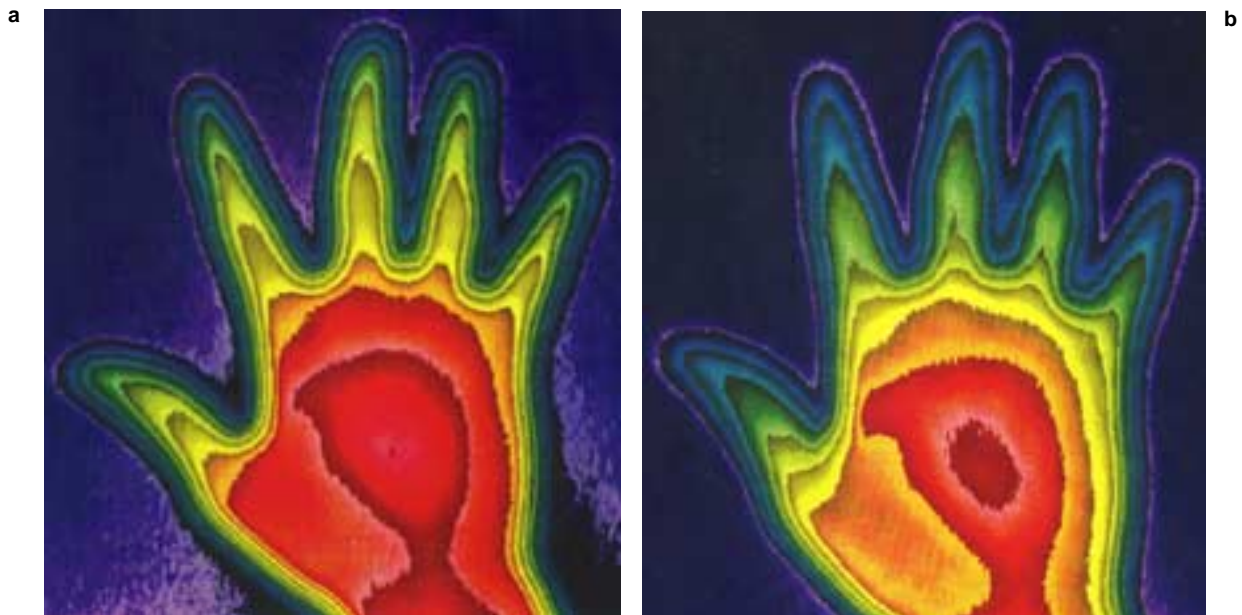
Fig. 11-4. These infrared images of a left hand in a cold environment demonstrate (**a**) the initial vasoconstriction of the hand exposed to a cold air environment (9°C). To the left of the image, the thermal scale ranges from 9.43°C to 35.68°C. Note the segmental nature of the vasoconstriction: the hotter parts are in the center. (**b**) Four minutes later at the same temperature, the digits of the same hand of the same subject have become very cold, with the palm becoming colder than it was initially. NOTE: infrared images record peripheral, not deep, temperatures.

Fig. 11-5. This infrared image is of the upper body of a person in an air environment of 19°C. The right hand (1) was placed in a glove until immediately before the picture was taken. The left hand (2) was not gloved. Note the extreme difference in vasoconstriction in the two hands. Selective vasoconstriction can also be seen in the neck and face, with the nose (3) vasoconstricting the most, followed by the cheeks, with the paranasal areas and the forehead staying warmer. NOTE: infrared images record peripheral, not deep, temperatures.

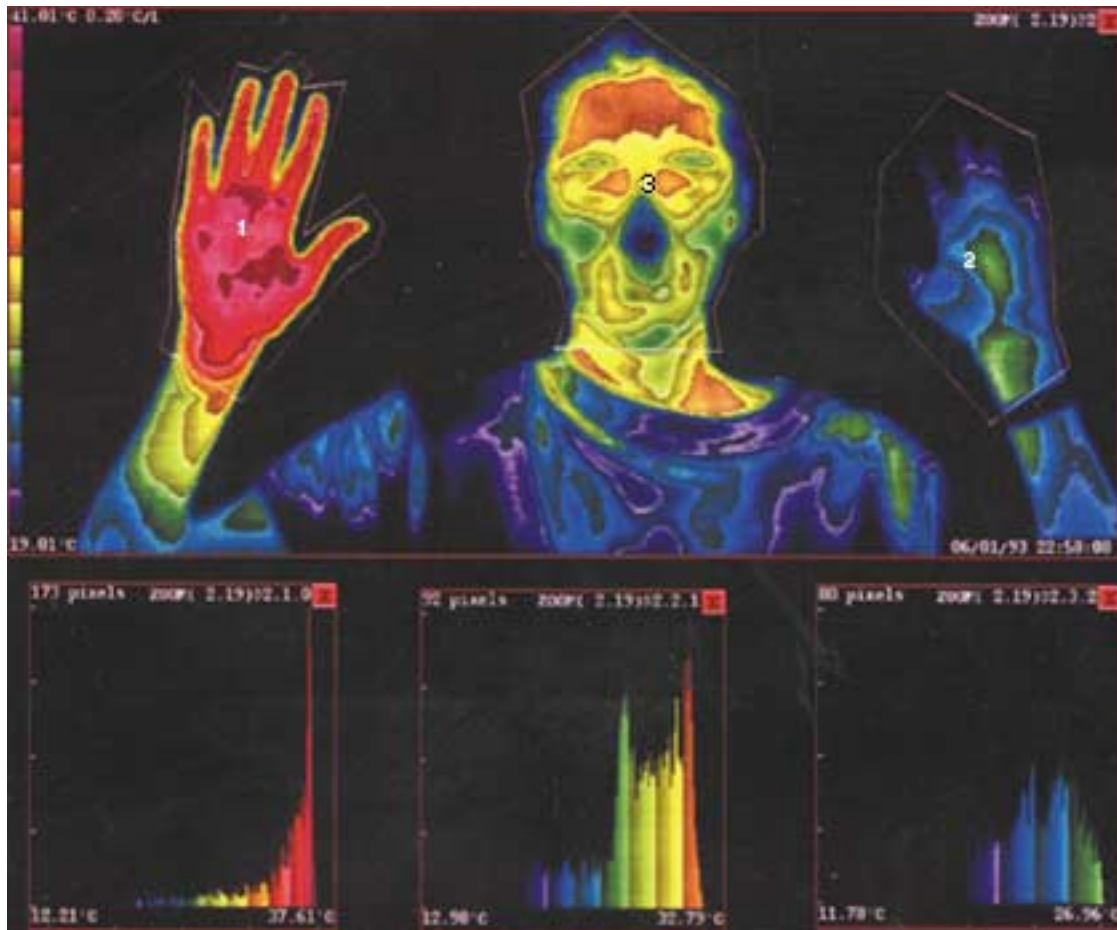cal agents influence peripheral vasoconstriction. Most military operations in cold weather are negatively affected by the pronounced discomfort associated with vasoconstriction of the extremities.

This representation is different from the classic one in that it demonstrates the power of the peripheral temperature in influencing core temperature.[27] From a practical point of view, in many cold weather operations, emphasis is placed on adequate hydration, sleep, nutrition, and clothing. Participants sometimes overdress, which leads to sweating and vasodilatation, which promote heat loss in a cold environment. Just as the physiological systems must constantly be increasing or decreasing various heat-producing mechanisms, so should the soldier who is in a cold environment. The major point is not to overdress, and at the same time to be aware of the insidious onset of hypothermia. This simple advice is difficult to implement, because the soldier must be able to withstand a wide range of temperatures. Thus, a bulky coat is usually issued.

The following discussion describes the effects of cold stress leading to hypothermia on major physiological systems (Table 11-1). Each physiological system has its own response to a decrease in core temperature, which create the signs of hypothermia (Exhibit 11-2). The challenge is understand that each of these systems interacts with every other. *Cold stress* refers to the body's response to cold, which, if not effective, will lead to hypothermia. In most field situations, the effects of cold are first felt in the extremities (feet, hands) and lead to frostbite; a more detailed presentation of the body's response to this stressor is found in Chapter 14, Clini-
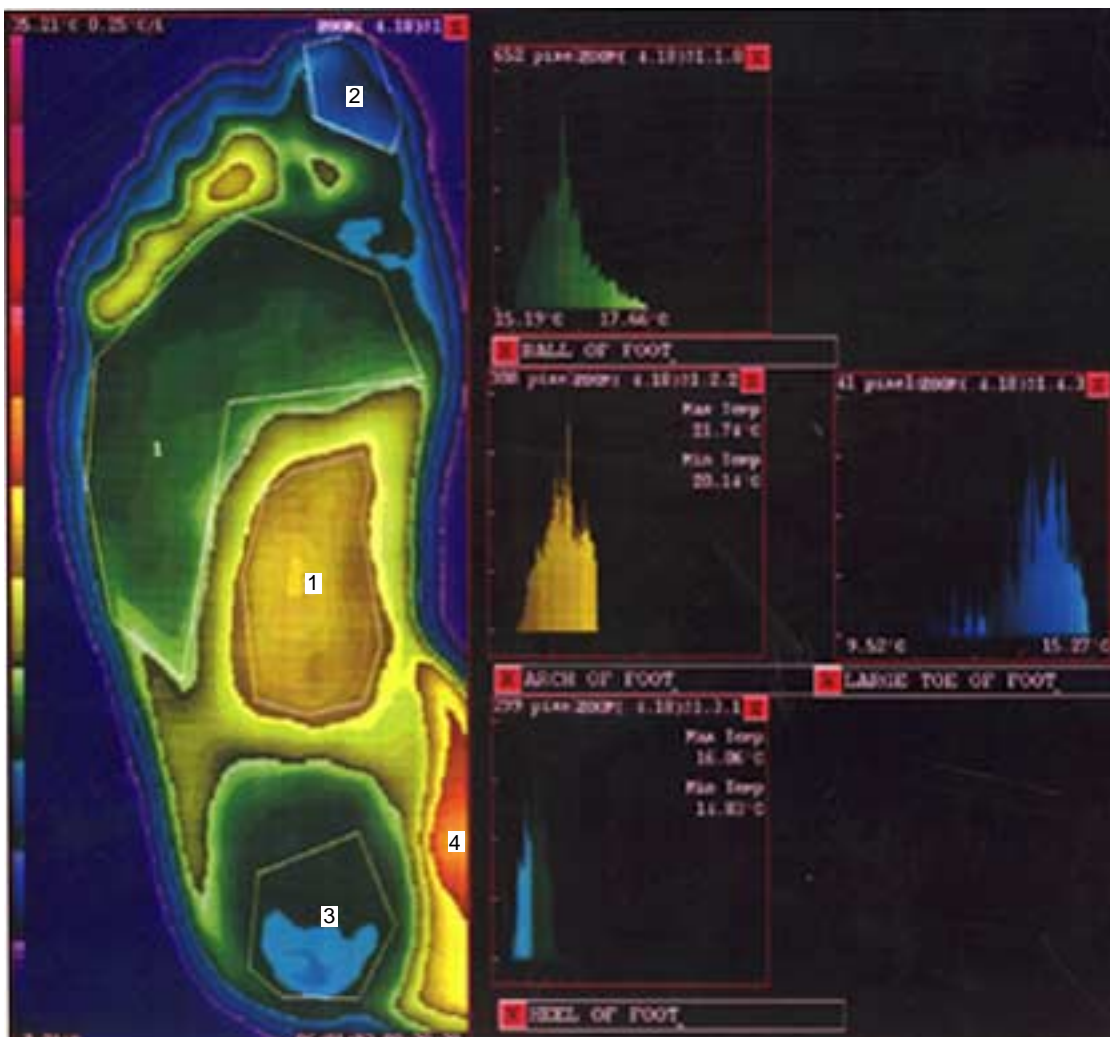
Fig. 11-6. This infrared image is of a subject's left foot, which was exposed to an environmental temperature of 7.0°C. The warmest part of the foot is the arch (1), whereas the toes (2) and heel (3) are vasoconstricted. The ankle (4) demonstrates a warm spot. NOTE: infrared images record peripheral, not deep, temperatures.

cal Aspects of Freezing Cold Injury. Hypothermia in the field represents a complete breakdown of logistical and medical support for field operations. The cardiovascular system is the most important physiological system concerning hypothermia, because the cold will eventually cause this system to break down. Although core temperature is important, the emphasis during rescue operations must be on evaluating and, if necessary, correcting cardiovascular and respiratory system function. Maintenance of adequate circulation and ventilation have a higher priority than thermal stabilization (Exhibit 11-3).

Central Nervous System

Many different anecdotal and field studies indicate that the first signs of hypothermia are disrup-

tion of higher functions such as visual and auditory hallucinations, and as the core temperature drops further, slurring of speech, decreased consciousness, and impairment of short-term memory occur. In one study,[28] local cooling of the inferior parietal lobe in a patient caused the patient to believe that his speech was being uttered by a stranger. It should be emphasized that these early signs might be the most critical for field operations, because they occur with mild hypothermia. In the field, monitoring an individual's behavior (by whomever is in charge, or a buddy) is more effective than attempting to measure the core temperature. Changes in an individual's behavior such as becoming withdrawn or silent may indicate the early stages of hypothermia. Consciousness is usually lost at a body temperature of 28°C to 30°C, but there are isolated

instances of persons still being able to talk when the core temperature was as low as 24°C.[29]

Although individual CNS neurons may be excited by a drop in temperature of one Centigrade degree, not all neurons are uniformly activated because the brain does not cool uniformly. This is demonstrated by a significant nonuniformity in temperatures in various areas of the brain in dogs, sheep, monkeys, and cats.[30] In addition, the anatomical organization of the cortical neurons may partially explain CNS changes associated with hypothermia. Some neurons have lengthy axons that extend to the periphery of the brain, and therefore cold temperatures will interfere with their electrical activity. Thus, neurons in the cortex with vertical extensions from the nerve cell body may have cold-induced multiple spikes.[31]

Eventually, hypothermia will cause a decrease in

TABLE 11-1

ALTERATION OF HUMAN PHYSIOLOGICAL SYSTEMS WITH DECREASING CORE TEMPERATURE

Stage	Core Temperature °C	°F	Characteristics
	37.6	99.6 ± 1	Normal rectal temperature
	37.0	98.6 ± 1	Normal oral temperature
	36.0	96.8	Increase in metabolic rate, blood pressure, and preshivering muscle tone
Mild	35.0	95.0	Urine temperature 34.8°C; maximum shivering thermogenesis
	34.0	93.2	Amnesia, dysarthria, and poor judgment develop; maladaptive behavior, normal blood pressure; maximum respiratory stimulation; tachycardia, then progressive bradycardia
	33.0	91.4	Ataxia and apathy develop; linear depression of cerebral metabolism; tachypnea, then progressive decrease in respiratory minute volume; cold diuresis
Moderate	32.0	89.6	Stupor; 25% decrease in oxygen consumption
	31.0	87.8	Extinguished shivering thermogenesis
	30.0	86.0	Atrial fibrillation and other arrhythmias develop; poikilothermia; pupils and cardiac output 67% of normal; insulin ineffective
	29.0	85.2	Progressive decrease in level of consciousness; pulse, and respiration; pupils dilated; paradoxical undressing
	28.0	82.4	Decreased ventricular fibrillation threshold; 50% decrease in oxygen consumption and pulse; hypoventilation
	27.0	80.6	Loss of reflexes and voluntary motion
Severe	26.0	78.8	Major acid–base disturbances; no reflexes or response to pain
	25.0	77.0	Cerebral blood flow 33% of normal; loss of cerebrovascular autoregulation; cardiac output 45% of normal; pulmonary edema may develop
	24.0	75.2	Significant hypotension and bradycardia
	23.0	73.4	No corneal or oculocephalic reflexes; areflexia
	22.0	71.6	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
	20.0	68.0	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19.0	66.2	Electroencephalographic silencing
	18.0	64.4	Asystole
	16.0	60.8	Lowest adult survival from accidental hypothermia[1]
	15.2	59.2	Lowest infant survival from accidental hypothermia[2]
	10.0	50.0	92% decrease in oxygen consumption
	9.0	48.2	Lowest survival from therapeutic hypothermia[3]

(1) DaVee TS, Reinberg EJ. Extreme hypothermia and ventricular fibrillation. *Ann Emerg Med*. 1980;9:100–110. (2) Nozaki RN, Ishabashi K, Adachi N. Accidental profound hypothermia. *N Engl J Med*. 1986;315:1680. Letter. (3) Niazi SA, Lewis FJ. Profound hypothermia in man: Report of case. *Ann Surg*. 1958;147:254–266.
Adapted with permission from Danzl D, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*. 3rd ed. St Louis, Mo: Mosby–Year Book, Inc; 1995: 55.

nerve conduction. For example, in human peripheral nerves, conduction velocity decreases from 30 m/s at 35°C to 12 m/s at 21°C. These decreases partially explain the observed motor incoordination and decrease in manual dexterity.[32] There will also be some cold-induced muscle stiffness and decrease in blood flow to the limbs, which contribute to the incoordination and loss of strength at that core temperature.

As core temperature continues to fall, cerebral metabolism decreases linearly from 6% to 10% for

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EXHIBIT 11-2

SIGNS OF HYPOTHERMIA

Psychiatric
  *Impaired judgment
  *Perseveration
  *Peculiar "flat" affect
  *Altered mental status
  Paradoxical undressing
  Neuroses
  Psychoses
  Suicide
  Organic brain syndrome
  Anorexia
  Depression
  Apathy
  Irritability

Cardiovascular
  *Peripheral vasoconstriction
  *Initial tachycardia
  Dysrhythmias
  Decreased heart tones
  Hepatojugular reflux
  Jugular venous distension
  Hypotension

Respiratory
  *Initial tachypnea
  Adventitious sounds
  Bronchorrhea
  Progressive hypoventilation
  Apnea

Musculoskeletal
  *Increased muscle tone
  *Shivering
  Rigidity or pseudo rigor mortis
  Paravertebral spasm
  Opisthotonos
  Compartment syndrome

Gastrointestinal
  Ileus
  Constipation
  Abdominal distension or rigidity
  Poor rectal tone
  Gastric dilation in neonates or in adults with
    myxedema
  Vomiting

Genitourinary
  *Polyuria
  Anuria
  Oliguria
  Testicular torsion

Neurological
  Depressed level of consciousness
  Ataxia
  Dysarthria
  Amnesia
  Anesthesia
  Areflexia
  Poor suck reflex
  Hypoesthesia
  Antinociception
  Initial hyperreflexia
  Hyporeflexia
  Central pontine myelinolysis

Dermatological
  *Erythema
  *Pallor
  *Cyanosis
  Icterus
  Scleral edema
  Ecchymosis
  Edema
  Perniosis
  Frostnip
  Frostbite
  Panniculitis
  Cold urticaria
  Necrosis
  Gangrene

Head, Eye, Ear, Nose, Throat
  *Rhinorrhea
  Mydriasis
  Decreased corneal reflexes
  Extraocular muscle abnormalities
  Erythropsia
  Flushing
  Facial edema
  Epistaxis
  Strabismus

*Usually occurs during the initial exposure to cold stress and hypothermia
Adapted with permission from Danzl D, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies.* 3rd ed. St Louis, Mo: Mosby–Year Book, Inc; 1995: 63.

each one Centigrade degree decrease in temperature from 35°C to 25°C.[31] Significant attenuation and frequency alterations in the brain's electrical activity can be observed at temperatures below 34°C.[33–35] Most importantly, prolonged hypothermia of the brain affects cerebral functioning in a descending manner, so that cerebral cortex function is initially impaired, followed by subcortical structures. When medullary cellular activity is suppressed, cessation of respiration follows. This hypothermia-induced apnea can be reversed by warming the fourth ventricle. Complete absence of electrical activity (a flatline electroencephalogram) normally occurs at temperatures below 20°C.

One of the challenges for medical officers involved in field operations in the cold is the fact that hypothermia will negatively affect an individual's performance but, paradoxically, once the person is hypothermic, the cold will transiently protect the brain from hypoxia. Fundamentally, it is still not clearly understood how hypothermia protects the brain from various hypoxic environments. Cooling the brain nonuniformly affects neural function, localized blood flow, and the integrity of the blood–brain barrier. Relative to other organ systems, a disproportionately high redistribution of blood flow is directed to the brain when profound hypothermia has occurred. Autoregulation of cerebral blood flow is maintained until brain temperature falls below 25°C. Part of the explanation of the cold-protective effect that hypothermia has on the brain is that it reduces vascular permeability in cerebrally nonischemic rats.[36] Decreasing cerebral temperatures minimized hypoxia-induced abnormalities in the blood–brain barrier in ischemic animals, whereas raising the temperature to 39°C exacerbated the abnormalities.[37] In addition, mild hypothermia reduced the degree of postischemic edema in gerbils after 40 minutes of bilateral carotid occlusion.[38] Overall, these studies suggest that hypothermia reverses the destabilizing effects of hypoxia on cell membranes.

Clinically, profound hypothermia is induced to minimize or prevent cerebral ischemic injury during certain types of cardiac and cerebrovascular surgeries.[39–41] The beneficial effects of clinically induced hypothermia classically have been attributed to a temperature-dependent reduction in metabolism.[35,42,43] As a result, whole-body circulation can be arrested for prolonged periods, exceeding 30 minutes, without incurring severe cerebral injury.[39,42,44]

The mechanism of neural protection associated with hypothermia is not clear. Profound hypothermia is not a strict prerequisite for neuronal protection, because significant cerebral protection may occur at mildly cold temperatures (33°C–34°C). Improved postischemic neurological function has been reported in animals in which mild hypothermia was instituted[45–48]; however, the neural sparing effect of hypothermia may not be related to the timing of the ischemic insult. Improved outcomes following ischemia were apparent even when the hypothermia was induced either during or immediately after the occurrence of the ischemic event.[45,46,49] Further complicating this area are the observations that mild hypothermia induces cerebral protection, which has not been correlated to a reduced production of lactate (ie, reduced anaerobic metabolism).[48,49] Hence, a hypothermia-induced reduction in global cerebral metabolism, per se, does not appear to be the complete explanation for the protective effects of mild hypothermia. Experimentally, the beneficial effects of mild hypothermia may be due to the following conditions[45,47,49]:

- a reduced metabolism,
- temperature-induced alterations in ion-channel function, which promotes calcium homeostasis (a major determinant of metabolism),

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EXHIBIT 11-3

PRIORITIZED RESUSCITATION REQUIREMENTS

1. Maintenance of tissue oxygenation:
   Adequate circulation
   Adequate ventilation

2. Identification of primary versus secondary hypothermia

3. Thermal stabilization:
   Conduction
   Convection
   Radiation
   Evaporation
   Respiration

4. Rewarming options:
   Passive external rewarming
   Active external rewarming
   Active core rewarming

Adapted with permission from Danzl D, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies.* 3rd ed. St Louis, Mo: Mosby–Year Book, Inc; 1995: 70.

- increased membrane lipid stability,
- alterations in the release and reuptake of neurotransmitters (eg, excitatory amino acids and dopamine),
- preservation of the blood–brain barrier, and
- the release of various substances that have a protective effect on cellular membrane function.

However, these results have to be considered relative to the experimental animal used, as species vary in their ability to withstand cerebral hypoxia and hypothermia. This area of research is at present one of the most active, because hypothermia in some form may act to protect the hypoxic, physically traumatized brain.

Motor Activity

From a military point of view, the effects of a cold environment have their greatest overt effect on the motor system. Troops are not able to move as fast, and fine coordination is impaired.[50] Cold hands make it difficult to pull a trigger or operate a keyboard. Cold stress and hypothermia influence motor function by way of the neural and cardiovascular systems and on the muscle cell itself. As a person is initially cold-stressed and then becomes hypothermic, muscle tension leads to shivering, which continues until core temperature reaches 29°C to 31°C. Preshivering tone, of which cold-stressed subjects are usually unaware, normally precedes shivering. In part, this tonic muscle activity is the basis for the feeling of stiffness that most people experience when they get cold.[51] Increased motor tone has been reported to appear first in extensor and proximal muscles, which are the same muscles in which the amplitude of shiver is largest.[52] However, humans vary greatly in their shivering patterns, with some human subjects shivering first in their chest muscles.

Shiver has been defined as involuntary rhythmic waxing and waning muscular contractions that are used to maintain a normal body temperature.[53] These oscillations are modulated by myotatic reflex loops, because deafferentation will cause the frequency characteristics of shiver to become irregular.[54,55] However, shivering can be influenced by cerebral cortex. A subject can temporarily turn off shivering by relaxing, doing exercises,[56] or modifying the breathing pattern. These techniques are invaluable for field operations, because they allow troops to conduct certain aspects of their mission even when they are cold-stressed.[52,57]

From a thermogenic point of view, shivering increases heat production 2- to 5-fold more than is necessary for normal body heat production. During different phases of shivering, both agonist and antagonist muscles contract periodically but not necessarily reciprocally. Thus there will be an increase in muscle tension, but the limbs do not move effectively. The frequency of shiver varies from muscle to muscle but is considered fairly low, between 5 and 10 Hz. In laboratory experiments, cold-stressed subjects will demonstrate synchronized muscle contraction of all muscles monitored. If the antagonistic muscles were to be coactivated at higher rates or to elicit contracture (ie, sustained force production without associated electrical activity), then the heat that could be generated would be proportionally greater. However, a major drawback to this type of activation would be the high degree of resultant limb stiffness that would limit one's ability to make superimposed voluntary movements.

The control mechanisms for shiver have both central and peripheral nervous system components. CNS shivering was produced by localized cooling of the hypothalamus.[58,59] Demonstrating the effect of peripheral temperatures on inducing shivering, Lim[60] reported that reducing subcutaneous temperature from 33°C to 30°C, while maintaining a brain temperature of 38°C, evoked a shivering response. Further supporting the role of peripheral regulation of the triggering of shivering are the observations that humans placed in a 10°C environmental chamber for 15 to 40 minutes demonstrate intense shiver—even though their core temperatures have not changed or are slightly increased.[61]

In a field situation, shivering is an important sign that all physiological systems are functioning (eg, cold receptors, hypothalamus, muscles), and also that hypothermia may eventually occur. If shivering persons are able to complain about the environment, more than likely they are cold-stressed or mildly hypothermic. Their ability to complain is an important sign that the troops may be in a critical situation, but they are not severely hypothermic—yet.

Respiratory changes have been documented to alter increases and decreases in shiver amplitude or changes in duration, or both. Inspiration of cold air causes an increase in rhythmic and tonic muscle activity, whereas inspiration of warm, humidified air can attenuate or stop spontaneous shivering.[62] When soldiers wish to minimize shivering, they should not inspire deeply. Although shivering generates heat and assists in minimizing a decrease in core temperature, it is not always desirable and may, paradoxically, influence a person's performance.

In many environmental situations, such as when a deep sea diver is trying to perform a fine-motor task, shivering is clearly undesirable. Attempts have been made to minimize the occurrence of such tremors during diving by employing specialized (ie, warmed) oxygen tanks to avoid hypothermia and prevent shiver. Although this technique minimizes shivering, it will not prevent the onset of hypothermia.

Cold environmental temperatures affect the muscles directly, protecting them when frozen. There are clinical case reports (discussed in greater detail Chapter 14, Clinical Aspects of Freezing Cold Injury) of individuals with frozen limbs who have been successfully rewarmed with no apparent long-term effects.

Circadian Rhythms and Sleep

Sleep deprivation is common in military operations. Because the sleep cycle and other circadian cycles are intimately linked, sleep deprivation might affect thermoregulation, as it does other neural systems, so as to cause visual hallucinations and impaired balance.[63] Although the sleep cycle influences thermoregulation by altering fundamental mechanisms in the CNS, the ambient temperature also influences these cycles.[64] An ideal situation for inducing hypothermia would be having troops with minimum food and water, isolated in a hostile, cold environment—such as a mountain—in which they cannot sleep.

THERMOREGULATION IN MAJOR PHYSIOLOGICAL SYSTEMS

Cold stress triggers changes in all physiological systems. As the drop in core temperature continues, all these systems demonstrate the effect of cold on the cellular metabolism of the organ, the blood flow, and neural activation. Understanding the effect of hypothermia on each system will allow the medical officer to be better prepared to assist the victim of hypothermia.

Cardiovascular System

The cardiovascular system has received the most attention in clinical studies of hypothermia because various surgical techniques, such as cardiac bypass surgery, have successfully employed low body temperatures. The reversibility of cold-induced ventricular fibrillation (cardiac arrest, or standstill) is one of the major determinants of survivability from hypothermia. A drop in core temperature will induce ionic alterations in cardiac muscle, such as hyperkalemia, which may induce cardiac standstill or fibrillation.[56,65]

Cold stress induces sympathetically mediated peripheral vasoconstriction, an increase in cardiac afterload on the heart, and elevated myocardial oxygen consumption. These changes are often associated with an initial tachycardia. As the core temperature continues to fall, bradycardia and myocardial depression occur, resulting in a decreased cardiac output and hypotension. In mild hypothermia, the variability in circadian heart rate is greater than during normothermia, possibly due to an imbalance between the parasympathetic and sympathetic nervous systems.[66]

A decrease in heart rate by 50% can be recorded from individuals with core temperatures near 28°C.[67] The lowered heart rate results from a decrease in the spontaneous depolarization of pacemaker cells and is refractory to atropine.[68] At core temperatures below 32°C, atrial dysrhythmia occurs, secondary to atrial distension.[69] Ventricular arrhythmias are commonly observed below 32.2°C, but primary ventricular fibrillation is rare at 32.2°C, with maximal susceptibility occurring between 28°C and 30°C.[70] At core temperatures lower than 30°C, the heart is very sensitive to mechanical stimulation, and cardiopulmonary resuscitation efforts may convert a very slow sinus bradycardia to ventricular fibrillation. As the core temperature approaches 25°C, fluid shifts out of the vascular space, which may increase the hematocrit by 150%.[71] The ensuing hypovolemia and increased blood viscosity further compromise the cardiac output.

An electrocardiogram demonstrates significant changes with hypothermia. These electrical changes are indicative of specific myocardial ionic activities that are influenced by the cold. Membrane currents are controlled by multiple processes that control the membrane channels, which are composed of lipoprotein and other chemicals whose activities are temperature-dependent. Thus, low temperatures result in both a slower activation and inactivation of different membrane currents, and they contribute to various electrophysiological changes. During hypothermia there is a prolongation of the PR and Q-T intervals and widening of the QRS complex. A significant drop in core temperature results in the reduction of the rate of depolarization, which in turn results in a widening of the QRS complex. The explanation for this phenomenon is that during hypothermia, the rate of the opening and closing of the sodium channels is decreased, and so-

dium-channel conduction is decreased as well, causing a reduction in the maximal rate of membrane depolarization. This phenomenon involves an interplay between various ions, such as sodium and potassium, because these ions have common transport mechanisms.

Hypothermia also influences the repolarization phase of the cardiac action potential. Due to alterations in various potassium currents, a drop of one Centigrade degree in myocardial temperature lengthens the cardiac action potential and refractory period by 15 to 20 milliseconds. During phase I of repolarization, there is an early transient outward potassium current. During phase III, there are two simultaneous temperature-sensitive currents: a time-dependent, delayed rectifying, potassium current and a time-independent, inwardly rectifying potassium current. When both of these repolarizing currents are reduced, a consequent lengthening of the action potential duration and refractory period occurs. Other inward currents, such as sodium and calcium, are also affected by hypothermia and contribute to the lengthening of the action potential.

Following depolarization, there is an opening of the voltage-dependent calcium channels, causing an influx of calcium ions, which in turn activates the release of calcium from internal storage in the sarcoplasmic reticulum. Subsequently, intracellular free calcium binds to contractile proteins, resulting in muscle contraction.[72] As a result, during the initial stages of hypothermia, systolic contractile force and intracellular calcium increase. This is due either to increased levels of free cytosolic calcium or to the increased sensitivity of the contractile proteins to calcium. Some investigators contend that cardiovascular collapse during hypothermia is not due to the irregularities of myocardial contraction but to reduced contractility or arrhythmia.[73]

The explanation for hypothermia-induced cardiac arrhythmias is not settled. The circus theory proposes that either a nonhomogeneous conduction or refractoriness, or both, may exist. As a result, there is a greater increase in conduction time than in the refractory period. Such an increase in the ratio of conduction time to refractory period makes reentry currents possible, resulting in ventricular fibrillation.[74] Another explanation is that nonhomogeneous thermal profiles result in disproportionate changes in refractory periods and conduction times. These cold-induced changes could easily produce multiple ectopic sites, eventually resulting in ventricular fibrillation.

Hypothermia affects the atria and ventricles differently. Because the speed of conduction is greater in the atria than in the ventricles, the pacemakers of the atrium will maintain normal synchronized muscle contraction at much lower temperatures. In contrast, because the conduction velocity in Purkinje's fibers is slower even at normal temperatures, the ventricles are more susceptible to being inhibited by the cold. This allows the ventricular myocardium to contract irregularly, promoting multifocal ventricular tachycardiac sites, and leading eventually to fibrillation or cardiac standstill. This difference in susceptibility is seen in rat hearts that have been stored at 4°C for 0, 12, and 24 hours.

Owing to the importance of hypothermia-induced ventricular fibrillation, much research has focused on the effect of cold on cardiac muscle and the conducting system in the heart, but interestingly, the effect of hypothermia on the coronary circulation has not received the same degree of study. There is little evidence that suggests that cold stress influences the responsiveness of the coronary arteries.[75] However, it is well recognized that angina pectoris (constriction of coronary arteries) can be either precipitated or worsened just by exposing the skin to cold[41]—a decrease in core temperature (à la hypothermia) is not required. Although current understanding has presumed that cold increases the metabolism of cardiac tissues by activating the sympathetic nervous system, this hypothesis has not been rigorously substantiated. In summary, the coronary circulation appears to respond to a cold stress as it would whenever cardiac output and systemic pressure increase through activation of the sympathetic nervous system.

Respiratory System

The initial respiratory response to cold stress is a significant increase in rate (ie, hyperventilation), followed by a decrease (ie, hypoventilation) (see Exhibit 11-2). Skin temperature afferents can influence respiratory function dramatically. Certain individuals will hyperventilate when they are exposed to a cold stress and others will not. The cold-stressed hyperventilation is followed by a progressive decrease in the respiratory minute volume that is proportional to the decreasing metabolism. The control of respiration becomes compromised as the function of the brain stem is impaired by severe hypothermia. Respiratory rate falls from 15 to 7 breaths per minute at 30°C to 7 to 4 breaths per minute at temperatures in the mid 20s.[76] Eventually, retention of carbon dioxide by the tissue leads to respiratory acidosis. In most cases of severe hypothermia, respiration diminishes and the heart continues to contract for some time.[77]

In field situations, the evaluation of respiration in victims of hypothermia is extremely challenging, as their slow breathing rate might be masked by environmental conditions (eg, wind, machine noise). Hypoxia can accelerate the decrease in core temperature. In a moderate cold-stress situation, hypercapnia lowered the threshold for shivering by 0.13°C and increased the core cooling rate by approximately 25%.[78] This decrease in core temperature may be due to the hypercapnic hyperventilation. This observation is important, because it demonstrates that in moderately cold environments, hypercapnia influences thermoregulation, whereas at very cold temperatures the body's response is so vigorous that it swamps the hypercapnic effect.

Stimulation of the respiratory drive by both carbon dioxide and hypoxia is absent at 20°C.[79] During moderate hypothermia, in an absence of shiver, a reduction in oxygen consumption is associated with a parallel reduction in carbon dioxide production. Thus, what would be considered low levels of oxygen pressure in normothermic environments would be adequate at hypothermic levels. Although in hypothermia the arterial content of carbon dioxide is low, the solubility of carbon dioxide has increased.

As an individual becomes hypothermic, several other physiological factors associated with respiratory function are influenced[80]:

- ciliary motility decreases,
- bronchorrhea is present,
- the potential for noncardiogenic pulmonary edema increases as fluid shifts occur,
- the contractile function of the diaphragm and intercostal muscles alters,
- lung compliance decreases,
- the elasticity of the thorax decreases, and
- anatomical and functional physiological respiratory dead spaces are increased, whereas individual alveolar dead spaces are unchanged.

Pulmonary circulation time is usually prolonged unless there is intrapulmonary shunting.

Although hyperventilation is associated with cold stress, cold-induced respiratory arrest also occurs. This reflex may be important in victims of submersion hypothermia. Such a response causes the person who is submerged to aspirate water and consequently drown. Simultaneously, the cold water aspirate rapidly cools the brain and heart, because the heart continues to beat effectively while pumping cold blood, for 5 minutes after aspiration.

The blood is rapidly cooled because it is circulated in the pulmonary cold water environment, dropping cerebral and cardiac temperatures. This rapid internal cooling is considered to be the explanation for the complete recovery of victims who experience cold water near-drowning. When a person nearly drowns in cold water, there are approximately 45 minutes during which the victim may be successfully revived. The rapid internal cooling of the internal organs, such as the brain and heart, allows the victim to survive hypoxia for approximately 45 minutes. This form of cooling is more effective in children than adults because they have a smaller mass and a large surface area–to-volume ratio. Not all victims who suffer from submersion hypothermia are successfully revived, however. Many remain comatose after heroic rescue and clinical attempts. This wide range of response may be due to a large number of variables, including the temperature of the water, the rate of cooling, the nature and quantity of the aspirate, and the clinical treatment.[81,82]

Renal System

Cold-induced diuresis is one of the early consequences of exposure to the cold, and it becomes prominent even before core temperature has decreased. The mechanisms for this cold-induced diuresis remain controversial.[83] One school of thought suggests that cold-induced diuresis is an autoregulatory response of the kidney to a relative central hypervolemia induced by peripheral vasoconstriction. Owing to a volume overload, the release of antidiuretic hormone is suppressed. The subsequent cold-induced diuresis decreases the blood volume so that progressive hemoconcentration develops.

The other explanation is that cold-induced diuresis may be due to osmotic alteration in the renal tubules. Renal function is eventually depressed during hypothermia owing to a fall in systemic blood pressure and the indirect effect of the cold on organ metabolism itself. As the renal blood flow decreases, renal vascular resistance rises, promoting a further decrease in renal flow and a subsequent decrease in glomerular filtration. During hypothermia, renal oxygen consumption is more rapidly reduced relative to other organs such as the liver, heart, brain, skeletal muscle, and skin. Serum sodium, calcium, chloride, and potassium concentrations remain in the normal range until core temperature is 25°C, but owing to the cold-induced depression of the renal tubular function, sodium and water reabsorption are reduced, promoting a pronounced osmotic diuresis.[84]

Faced with continuous hypothermia, an additional large shift of body water will occur. Whether the cold-induced diuresis is explained on the basis of volume overload or ionic imbalances, it is a major concern. For example, cold water immersion has been shown to increase urinary output by 3.5-fold, and this decrease in body water may be a factor contributing to the "rewarming shock" that occurs following active vasodilation induced by rewarming treatments.[85] Potassium ion regulation may be impaired in hypothermia. Hyperkalemia, one of the leading causes of cardiac dysrhythmia,[80] is usually an ominous sign of tissue hypoxia.[86]

From the practical standpoint in the field, one of the only ways to assess hydration is to examine the color of the urine. Most military units insist on visually inspecting the degree of darkness of each individual's urine. The more hydrated the individual, the less dark the urine (see Figure 5-5 in Chapter 5, Pathophysiology of Heatstroke).

Blood

As hypothermia decreases cellular function, the amount of oxygen available remains constant because the oxyhemoglobin dissociation curve shifts to the left. This shift is physiologically very important, as it dictates that the partial pressure of oxygen must fall to lower values before hemoglobin gives up its oxygen.[87] Thus, hypothermia induces a physiological bank of oxygen. In the face of hypoxia, cells shift to anaerobic metabolism, resulting in a metabolic acidosis. As hydrogen ions enter the blood, they shift the oxygen dissociation curve to the right, which promotes the unloading of oxygen. Thus we can say, simplistically, that hypothermia protects various organs because hypothermic organs have decreased oxygen demands, while simultaneously, adequate oxygen is available to meet those reduced metabolic demands.

Contributing to the therapeutic effects of hypothermia is the fact that both oxygen and carbon dioxide are more soluble in cold blood. Compared with normothermic values, the solubility of oxygen is increased by 33% at 25°C. Although this increase in solubility cannot be considered an added benefit until the temperature of the tissue falls to 16°C,[88] it nevertheless allows for oxygen to be available to the hypothermic cells.

Another important but deleterious consequence of hypothermia, particularly for combat casualty care, is that clotting time is prolonged. This is because enzyme reaction times are reduced, which slows clotting time, and because the platelets are sequestered in both the portal circulation and the liver. In addition, an elevation in hematocrit and viscosity occur.[88] Patients with clinically induced hypothermia, as measured by tympanic probes, experienced blood loss 0.5 L greater than that of normothermic patients, leading some investigators to argue for minimizing mild hypothermia during surgery.[89]

Acid–Base Balance

The most important, yet controversial, area of hypothermia is the clinical treatment of acid–base imbalance. Although the decrease in core temperature is considered the important physiological *consequence* of a cold stress, the key physiological *element* is the control of hydrogen ion concentration. Acid–base balance in hypothermic situations differs from that in normothermia. Owing to the variety of underlying causes of hypothermia, clinical prediction of acid-base status is not possible. In one series of 135 cases, 30% of patients were acidotic and 25% were alkalotic.[90] After an initial respiratory alkalosis from cold-induced hyperventilation, the more common underlying disturbance is a relative acidosis. Acidosis has both respiratory and metabolic components. From a respiratory perspective, as the temperature decreases, the solubility of carbon dioxide in blood increases. Metabolic acidosis is produced by impaired hepatic metabolism and acid excretion, lactate generation from shivering, and decreased tissue perfusion.

How should a medical officer correct a hypothermia-induced pH profile? Confusion persists regarding arterial blood gas pH correction relative to the reduction in core temperature. Initially, to aid the clinician's interpretation of the pathophysiology involved in hypothermic arterial oxygenation and acid–base balance, the pH was corrected to normal values for body temperature.[91] This approach created problems. If a pH electrode was used at the casualty's current core temperature, an uncorrected but exact pH value would be obtained. However, arterial blood samples are always warmed to 37°C before electrode measurements are obtained and are not measured at the patient's subnormal temperature.

Optimal clinical strategy to maintain acid–base homeostasis during treatment of accidental hypothermia is still evolving.[92] The practical clinical problem is of some importance in cardiac surgery, however, where there is considerable experience with hypothermia during cardiopulmonary bypass. The assumption that was accepted earlier was that 7.42 is the ideal, "corrected" patient pH at all tem-

peratures, and that therapy should be directed at maintenance of the corrected arterial pH at 7.42. The approach for maintaining this pH level, termed "endothermic," has been questioned.[89] A better intracellular pH reference may be electrochemical neutrality, in which pH = pOH. Because the neutral point of water at 37°C is pH 6.8, Rahn and colleagues[93] hypothesized that this normal 0.6-unit pH offset (7.4 – 6.8) in body fluids should be maintained at all temperatures. Because the neutral pH rises with cooling, so should blood pH. This pH approach, termed "ectothermic," is commonly followed.

Previously, Rahn[94] had observed that Antarctic codfish survive far below the freezing point of water (owing to a presence of glycoprotein that minimizes formation of ice crystals [antifreeze]), and they continue to function in an extremely alkalotic state. This same blood pH variation (ie, a rise in pH with a decline in temperature) is found in other cold-blooded vertebrates and invertebrates. Several experimental and clinical studies support Rahn's hypothesis. In one study,[95] a set of puppies with pH maintained at 7.4 had a 50% drop in cardiac performance after bypass. The control group, left alkalotic, had normal cardiac indices and increased cerebral blood flow. In another study[96] with canines during systemic deep hypothermia, constraining the correct pH to 7.4 caused myocardial damage, whereas relative alkalinity afforded myocardial protection. Other advantages of relative alkalinity include improved electrical stability of the heart. The fibrillation threshold of dogs markedly decreased when arterial pH was held at 7.4 but was unchanged with alkalosis. In contrast, maintaining the pH at 7.4 during hypothermia in a rat model did not affect cardiac work response.[97] These data suggest that the optimal range of extracellular pH is large in some species.

Supporting the view that the alkalotic state is beneficial to hypothermic patients is a study by Kroncke and associates,[98] in which they studied 181 patients who had cardiac bypass surgery, 121 consecutive cases of whom were "endothermically" managed with corrected normal pH and P_{CO_2} (partial pressure of carbon dioxide) values. Ventricular fibrillation occurred in 49 (40%). The remaining 60 patients were left "ectothermically" alkalotic; of these, only 12 (20%) developed spontaneous ventricular fibrillation.

These observations provide some evidence in support of Rahn's hypothesis, that the advantage that ectotherms obtain with a constant relative degree of alkalinity also applies to warm-blooded endotherms during hypothermic conditions. Poten-

tially deleterious effects of alkalosis on other systems have yet to be identified. However, on the acidotic side, it is clear that maintaining the corrected pH at 7.4 and P_{CO_2} at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow and cardiac output, and increases the incidence of lactic acidosis and ventricular fibrillation. Correction of pH and P_{CO_2} in patients with hypothermia is unnecessary and potentially deleterious. This last statement is pertinent to field rescue operations. Owing to the complexity of the interaction of the causes of hypothermia, as well the acid–base stabilization, it is always advisable to minimize heroic efforts in the field to rewarm hypothermic casualties and correct their pH, unless they can be properly evaluated and medically managed. Raising the body temperature or attempting to correct the pH level in blood, or both, might cause potentially deleterious changes in blood pH, leading to ventricular fibrillation.

Fluid and Electrolyte Balance

Dehydration is usually associated with hypothermia, with free-water depletion elevating serum sodium and osmolality. Because hypothermia produces natriuresis, saline depletion may be present.[69]

Blood viscosity increases 2% per degree Centigrade drop in temperature, and hematocrits higher than 50% are seen. During rewarming, low circulatory plasma volume is often coupled with elevated total plasma volume.[99]

Infusion of fluid does not always reverse hypothermia-induced fluid shifts. In one set of experiments,[98] normal saline had minimal lasting effects and did not hasten cardiovascular recovery from hypothermia. In another study,[100] 10% low molecular weight dextran solution increased plasma volume and decreased blood sludging.

In some patients with hypothermia, rapid volume expansion is critical.[101] In neonates, adequate fluid resuscitation markedly decreases mortality.[65]

Gastrointestinal System

Gastrointestinal smooth muscle motility decreases as core temperature falls, resulting in acute gastric dilation, paralytic ileus, and distension of the colon. In addition, all gastrointestinal secretions and free acid production are depressed.[69] The pancreas and the gastric mucosa are major sites of the cold-associated hemorrhages called Wischnevsky's lesions,[102] which are seen in 80% of victims of hypothermia and are of greater severity in younger

individuals. These lesions may be the result of reperfusion after cold-induced collapse of the microvasculature. Hypothermia causes a catecho---l-amine-induced vasoconstriction of blood vessels and release of corticosterone, which can be ulcerogenic. Eventually catecholamine secretion is decreased, promoting a vasodilatation that results in significant reperfusion and eventual extravasation of blood. The reperfusion and associated changes alter the gastric mucosa's protective mechanism, resulting in cellular damage induced by hydrochloric acid.

Hypothermia causes a decrease in splanchnic blood flow, which may be greater than the proportional fall in cardiac output.[103] Liver cells continue to metabolize but are not able to utilize glucose. Associated with the depression of liver function will be a significant decease in its ability to rid the body of metabolites, drugs, or conjugate steroids. Simultaneously, the other cells in the body are also inactivated by the cold. Thus, the drugs' target cells will not metabolize the drugs. This fact explains why various drugs have a reduced effect in hypothermic individuals, and explains the failed attempts of drug-induced suicide in hypothermic victims.

Endocrine System

Cold stress and hypothermia are major stressors and evoke a widespread hormonal response. Exposure to cold will stimulate the release of catecholamines, which will stimulate thermogenesis.[104]

Corticosteroids also become elevated. There is an inverse relationship between the concentration of 11-hydroxy-corticosteroids in plasma and the depth of hypothermia. In one study,[105] the highest concentrations of corticosteroids (96.4 µg/dL) were measured in hypothermic individuals who died, whereas those who died 3 days later had corticosteroid values of 87.1 µg/dL, and those who survived had the lowest levels, 62.9 µg/dL. However, in another study, Stoner and colleagues[106] did not find any correlation between plasma cortisol concentration and core temperature with respect to survivability. Thyroid-stimulating hormone (TSH) and thyroid hormone concentrations have been recorded as normal in hypothermic patients. With rewarming, concentrations of thyroxine (T_4) and triiodothyronine (T_3) concentrations decreased: T_4 concentrations were 8.2 µg/dL and decreased to 7.0 µg/100 dL, and T_3 concentrations decreased from 155 µg/dL to 138 µg/dL.[107]

Insulin concentrations in hypothermic patients vary. Insulin's role in facilitating the transport of glucose into cells becomes inactive below 31°C, and yet at these temperatures blood glucose concentrations are noted to be variable. Prescott and colleagues[108] reported that some hypothermic patients were actually hyperglycemic, but these patients had diabetes and severe ketoacidosis. In general, the blood glucose concentration depends primarily on the metabolic state of the patient and not on the degree of hypothermia. The control of glucose levels in hypothermic states is far from understood because pancreatitis is a common finding at autopsy of hypothermic individuals.[109] The extent of hyperglycemia is proportional to the degree of body cooling. Depending on the degree of hypothermia, the hyperglycemia may be due to (1) an increase in catecholamine secretion, (2) a decrease in insulin activity, (3) a decrease in renal clearance of glucose, (4) a decrease in liver enzyme function, and (5) an increase in catecholamine-induced glycogenolysis. Information concerning protein and fat metabolism during various levels of hypothermia is lacking.[41]

Ethanol ingestion inhibits glucose-induced insulin secretion and stimulates pancreatic glucagon secretion. Overall, ethanol will lower blood glucose concentration and impair gluconeogenesis. Hypoglycemia associated with exercise will promote a faster rate of hypothermia.[110] Thus, military attention to proper diet in cold weather operations is critical. Giving alcoholic drinks to victims of hypothermia may make them feel better, owing to the anesthetizing effects of the alcohol, but will inhibit their natural heat-generating mechanisms.

Immune System

The effect of hypothermia on the immune system is rarely considered in reviews. In a real-life scenario, hypothermia is usually associated with infections that might compromise the tolerance of the victim. In controlled cold stress or hypothermic studies—in either Department of Defense laboratory or military field experiments in which the subjects were previously screened for illness—the hypothermic subjects rarely became sick. In an extensive number of hypothermic studies conducted at the University of Minnesota in which more than 250 medical students were made mildly hypothermic, none became ill following a 3-week period of evaluation. However, in both hospitals and field operations, in which various stressors interact to compromise the immune system, hypothermia and infection go hand in hand.

Everyday experiences demonstrate that decreased ambient temperature inhibits immune function. When a soldier injures a joint, for instance, ice

is used to prevent the infiltration of immune cells and the subsequent release of inflammatory cytokines. Conversely, heat can be applied to abscesses to speed healing. A more dramatic example would be the high propensity of leukopenia and bacterial infections in children kept hypothermic for clinical reasons.[111] Although advances in immunology have not yet been integrated with existing knowledge of hypothermic sequelae, unanticipated nonthermal positive effects may be seen.[112]

Fever augments immune function[113,114] because hyperthermia of two Centigrade degrees above normal core temperature temporarily raises the mononuclear cell count in patients with cancer and increases the mitogenic response.[115] Thus, an increase in body temperature, whether induced or spontaneous, can confer an advantage to the immune response.

On the other hand, decreases in core temperature are detrimental to immune function, as opposed to having merely a neutral effect.[114] Sessler and colleagues[116] demonstrated that wounds are larger in guinea pigs that are infected under hypothermic conditions than in those infected under control conditions. Because more than half of the body volume is 1 inch from the surface and significantly cooler than the core body temperature of 37°C,[117] local skin temperatures may influence the growth of infections. Vasoconstriction lowers resistance to infection by decreasing the partial pressure of oxygen in tissues.[118] This decrease in oxygen pressure decreases oxygen- and nitrogen-containing free radicals, both of which play major roles in microbial killing.

One explanation for cold-induced immunosuppression is that the immune cells are specifically inhibited by decreased temperature. In cases of secondary hypothermia, when thermal compensatory mechanisms become inadequate, certain observations can be made about the effect of cold on specific populations of immune cells. Histamine release from type I mast cells is decreased at low temperatures,[119] and Biggar and colleagues[120] showed that neutrophils were impaired in their migration, both in vivo and in vitro, at reduced temperature. When the cooled cells were rewarmed, they exhibited optimal activity. In a clinical study,[121] hypothermic patients (as assessed by tympanic temperature) who had undergone colorectal surgery had more surgical wound infections and their sutures were removed 1 day later than patients who were given additional warming. Peripheral vasoconstriction was seen in 78% of the hypothermic patients versus 22% for the normothermic group.[121] From a military perspective, there was another interesting finding: three times as many infections were found among smokers in both groups. Minimizing smoking among troops might do as much to minimize infections postoperatively as efforts to rewarm patients who are mildly hypothermic.

Wang-Yang and colleagues[122] reported that some in vitro responses of helper T cells in mice are inhibited by cold, but that B cells were not similarly suppressed. Cold interfered with interleukin (IL) production in virgin helper T cells, implying an early block in the activation of these cells. However, the responses of these cells to IL-2 and IL-4 were not affected by cold.

One of the most compelling, yet challenging, aspects of immunology is to understand the mechanisms by which individual parts integrate into a functional whole. Limited studies have addressed this important issue. Corticosteroids, which are released during cold stress, hypothermia, or both, have a well-documented immunosuppressive effect.[123] When cold stress is applied to an animal, specific changes in the cellular components can be observed. Sundaresan and colleagues[124] showed that when albino rats were subacutely stressed with cold water immersion, the total number of immune cells was initially expanded. Total white cell count was increased, as were total numbers of eosinophils and basophils. Phagocytic and avidity indices were also increased in phagocytic cells. However, Cheng and colleagues[125] showed that prolonged cold water stress actually has an immunosuppressive effect: they reported a decreased number of thymocytes and splenocytes, as well as diminished blastogenesis of T cells and lowered activity of natural killer cells. Macrophages were found to be less responsive to interferon gamma, and because these antigen-presenting cells are crucial for initiating immune cascades, the impairment of macrophage function could be a significant cause of a dampened immune response. While the mice in the Cheng experiment were obviously also stressed by anxiety and exercise, these results have implications for many settings of human accidental hypothermia.

Aarstad[126] reconfirmed the results of Cheng, in that an absolute value of cluster of differentiation 4+ (CD4+) cells, which are most commonly considered to be helper T cells, was affected by cold stress, but not that of CD8+ cells, which are most commonly considered to be killer T cells. In the Aarstad experiments, the number of stressors per day, as well as the duration of the trial, were varied and had an effect on the various populations of cells. For example, mice stressed once a day actually showed an increase in the percentage of CD4+ cells,

while the mice stressed twice a day showed a decrease.

Current data suggest that the immune system is significantly impaired in hypothermic settings. Some studies, however, indicate the contrary: that antibody–antigen interactions may actually be stronger at colder temperatures. Further, the optimal working temperature of complement is said to be 20°C to 25°C.[127] However, as was previously reiterated, many of the cell-mediated responses and the microenvironmental conditions that are critical to an active immune response are made defective by cold. To emphasize what has been presented, two of the more important players for initiating an immune cascade, helper T lymphocytes and macrophages, are specifically inhibited by cold.

Finally, it is also important to consider the microvasculature changes to cold, both local and throughout the body. Viscosity of the blood increases with cold, due in part to the aggregation of red blood cells and the increased adhesion of white blood cells to the endothelium.[128] Capillary occlu-

sion is possible, leading to hypoxic damage. Endrich and colleagues[128] report a result different from many others; namely, an observed increase in the permeability of the chilled vessels to macromolecules, leading to some leukocyte extravasation before the increased adherence of these cells. Overall, cold affects the immune response not only by inhibition of specific cells but also through blood cell and vascular changes, such as alterations in viscosity of the blood and permeability of the vessels.

Acclimation may play a major role in attenuating a response to an acute cold stress. Kizaki and colleagues[129] reported that in response to an acute cold stress, cold-acclimated mice exhibited a significant attenuation of the increases in serum corticosterone levels and the expression of the GC-receptor messenger RNA on peritoneal exudate cells. If one can extrapolate from these studies to humans, it is conceivable that humans who are acclimated to cold may be able to withstand a cold stress and minimize any major alterations in their immune response.

MILITARILY RELEVANT ISSUES

There are several militarily relevant aspects of managing the cold casualty in the field, including resuscitation, rewarming, and human tolerance to cold environments. Medical officers should keep in mind that the time available to resuscitate hypothermic casualties is prolonged because of their slowed metabolism. As the familiar saying implies, "You are not dead until you are warm and dead."[130] In addition, we should never underestimate the difficulty of carrying out seemingly simple interventions in a combat zone. It is clear that still-unresolved problems of field resuscitation are areas in which the military medical research establishment can play an important role.

Resuscitation and Rewarming

Chapter 14, Clinical Aspects of Freezing Cold Injury, contains an extensive discussion concerning various rewarming modalities in the field and in the hospital. In many situations, military personnel may be faced with rewarming a person in the field. For mild hypothermia, having the person drink warm fluids and removing him or her from a cold environment should be more than adequate. After approximately 30 minutes of mild hypothermia, mild exercise is a very effective way to rewarm a victim of hypothermia. However, in certain situations, rewarming involving external methods may

be implemented. Exhibits 11-4 and 11-5 list major rewarming techniques and contraindications to cardiopulmonary resuscitation (CPR) that any rescue group needs to consider. In a field operation, the options for rewarming are limited, and many methods of rewarming that have been proposed over the years may not be effective.

One point should be emphasized: body-to-body rewarming is *not* an effective technique. Giesbrecht and colleagues[131] reported that in humans who were made mildly hypothermic by immersion, shivering in a sleeping bag was just as effective as body-to-body rewarming. In fact, the hypothermic subject's shivering was blunted by body-to-body rewarming. In their conclusions, the authors recommend that subjects who are mildly hypothermic should be removed from their environment and rewarmed. In the field, when logistical considerations prevent evacuation, they recommend any form of external heat, including direct body-to-body contact. Such a recommendation is fraught with a number of problems. Over the years, victims of hypothermia have been found together in a sleeping bag, dead. More than likely, these deaths were a consequence of the mistaken assumption that one person can adequately rewarm another who is hypothermic. If the hypothermic individual is shivering, the addition of a warm body will suppress shivering. If the victim is severely hypothermic and is not shivering,

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EXHIBIT 11-4

REWARMING TECHNIQUES*

- Endogenous Rewarming
  - Basal metabolism
  - Shivering
  - Exercise

- Passive External
  - Thermal stabilization
  - Insulation

- Active External
  - Radiant heat*
  - Hot water bottles*
  - Plumbed garments*
  - Electric heating pads and blankets*
  - Forced circulated hot air*
  - Immersion in warm water*

- Active Internal (Core)
  - Inhalational rewarming
  - Heated infusions
  - Lavage
    - Gastric and colonic
    - Mediastinal
    - Thoracic
    - Peritoneal
  - Extracorporeal blood rewarming
  - Diathermy

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*Many methods of rewarming that have been proposed over the years may not be effective in the field, using core temperature change as the key criterion. Logistical ease of use and physiological effectiveness need to be evaluated before the techniques are fielded.

Adapted with permission from Danzl D, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies.* 3rd ed. St Louis, Mo: Mosby–Year Book, Inc; 1995: 72.

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the addition of one warm body will not be adequate to rewarm the subject. Also, rewarming may induce rewarming-induced core temperature afterdrop, leading to rewarming collapse (discussed below). Unsubstantiated studies of body-to-body rewarming practices suggest that three normothermic, seminude subjects be placed around the seminude victim of hypothermia, all four in interconnected sleeping bags. Such a solution is neither practical nor recommended, but it does emphasize the fact that one person, no matter how warm, cannot warm a victim of severe hypothermia.[132]

Core Temperature Afterdrop and Rewarming Collapse

The major problem facing the transport of victims of hypothermia is the fact that any form of rewarming may induce major pathological responses of the cardiovascular system, leading to what is called *rewarming collapse*. This problem is so controversial and difficult to control in the field that some have advocated that (1) any hypothermic victim should simply be removed as quickly as possible to a hospital site and (2) minimal efforts should be taken to rewarm the subject in the field. *Core afterdrop* refers to the additional decrease in core temperature that can occur when a hypothermic individual is removed from the cold exposure. The importance of core afterdrop is that, if severe enough, it will trigger syncope and even ventricular fibrillation. Core afterdrop and its effects may be the major explanation for the deaths of victims of hypothermia after they have been rescued and rewarmed.

Core afterdrop has two major mechanisms of action: conductive and convective. As a person becomes hypothermic, a temperature gradient is established between the cooler periphery and the warmer core. Each layer from the core to the periphery is cooler than its immediately superficial layer. When a person is rewarmed, the temperature gradient is reversed, but the temperature of each layer from the core out to the periphery will continue to fall until the layer just superficial to it is warm. This phenomenon has been seen in both inanimate and animate objects.[133] However, afterdrop has another component. As victims of hypothermia are warmed, the process causes their peripheral blood vessels to

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EXHIBIT 11-5

CONTRAINDICATIONS TO CARDIO-PULMONARY RESUSCITATION IN ACCIDENTAL HYPOTHERMIA

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1. Rescuers are endangered by evacuation delays.
2. Obviously lethal injuries are present.
3. Chest-wall depression is impossible.
4. Any signs of life are present.

Source: Danzl DF, Pozos RS, Auerbach PS, et al. Multicenter hypothermia survey. *Ann Emerg Med.*

dilate; the dilated blood vessels then act as conduits for relatively warm core blood to be carried to and cooled by the periphery. A greater afterdrop has been seen in studies[134] in which hypothermic subjects have been gradually rewarmed with increasingly warmer water, which causes greater vasodilation. Thus, from a practical point of view, the faster a hypothermic victim is warmed, the greater will be the afterdrop.[134] Because the number of unknown factors is large, medical officers need to keep in mind that the rewarming of severely hypothermic casualties in the field might induce rewarming collapse.

Another controversial area is the appropriateness of CPR in the field. As previously suggested (see Exhibit 11-5), there are times when CPR may not easily be implemented in the field. The first point listed, that the rescuers themselves should not be endangered by evacuation delays, should be emphasized.

Predictions of Human Tolerance in Cold Environments

As was previously mentioned, attempts have been made to model human thermoregulatory responses in cold environments and to arrive at times for various stages of hypothermia to begin. The complex interaction of various environmental, clothing, and physiological factors allows for the generation of such cooling curves to be extremely conservative. The physiology of the hypothermic individual varies with the degree of core cooling, which does not permit simplistic modeling. For example, individuals whose core temperature falls at a rate of 1.5°C per hour and who breathe 4% carbon dioxide lose core temperature faster than controls.[78] However, if the rate of cooling is three Centigrade degrees per hour, the effect of carbon dioxide is not noticed. The use of various agents (eg, herbs, drugs) has not been extensively studied for effectiveness in enhancing metabolic rate or resistance to cold stress. Nevertheless, in military communities such agents are routinely rumored to be effective—but without a shred of scientific data.

Because it is unethical to mimic various combined stressors (which may be lethal) in human subjects, anecdotal evidence and clinical case histories are the sole sources of survival and endurance data. Although lacking rigorous scientific controls, these sources may suggest various levels of human endurance and may give insight into various other mechanisms that might be at work as a person becomes hypothermic.[130] Furthermore, single case histories are valuable because they present issues that may never appear in a controlled laboratory situation. A specific example of physiological insight gained from field experiences is paradoxical undressing, which is associated with many dead victims of hypothermia. The cause of the undressing is unknown, but it indicates an area of additional research. A note of caution is warranted, however. Rescuers should be wary of undocumented anecdotal stories of persons who can withstand extremely cold environments for prolonged periods. Most of these cases, when studied thoroughly, suggest that the stories are fraught with contradictions or outright falsification.

Challenges for the Military in Future Cold Weather Operations

Although the basic mechanisms of thermoregulation in a cold environment are well documented, there are a number of unanswered physiological questions and challenges that military medical science will have to address. From a military perspective, with the possibility of chemical–biological warfare ever present, the greatest threat to military personnel will be to protect themselves from these agents. Thus, soldiers in cold weather operations who are enclosed in mission-oriented protective posture (MOPP 4) gear face a number of hazards: (1) the toxic environment, (2) the dangers on the battlefield, (3) the build-up of core temperature as they are encapsulated in impermeable protective clothing, and (4) decreased core temperature as their peripheral and core temperatures fall when they remove the MOPP 4 ensemble.

A simple, lightweight microclimate cooling system may be required for soldiers conducting cold weather operations. In the future, many of the soldier's physiological systems (eg, heart rate) will be monitored in the field, and the data will be transmitted to remote sites. A technical system that allows for the monitoring of core temperature in the field is required. Although some systems are available to perform this function, most do not give a robust or consistent recording and are not field hardened. Because most troops must be prepared for 24-hour deployment worldwide, they will not be acclimatized to either hot or cold temperatures. (For a thorough review of human cold acclimatization, interested readers may consult Young's chapter in the *Handbook of Physiology*.)[135] Constant exercises in the cold are required for maintaining combat effectiveness for cold weather operations. Although more "hot spots" are thought to be in hot climates, and hyperthermia may be considered a greater

problem than hypothermia, history teaches us that wars or peacekeeping operations occur in unexpected places (eg, Bosnia, Serbia, North Korea).

Possibly the greatest challenge for cold weather military operations will be to adequately train and teach personnel the straightforward facts about the body's robust response to cold stress. Ignorance about cold stress may be as lethal as any toxic material in the cold environments in which the military conducts its operations.

SUMMARY

Cold environments have proven to be the nemesis of many a well-planned military campaign. The insidious nature of the decrease in core temperature is the fundamental underpinning of the induction of mild to moderate hypothermia for supposedly well-trained and well-prepared military troops. Because the military has personnel who come from various geographical regions, the ability to use only specifically designated troops for cold weather operations is not practical. The military has researched various ways to minimize the onset of hypothermia by evaluating various kinds of cold weather gear and cold weather rations, as well as by understanding the physiology of cold response and the pathophysiology of hypothermia. Although it is often stated that there is nothing to research in the area of thermoregulation in the cold, many practical observations indicate that there are areas of research that are critical for effectively performing military operations in cold environments. The military has pioneered the use of models to predict the onset of hypothermia. However, the variability in human response based on the physiology of the troops makes this a laudable but not achievable goal in the real world.

The control of the core temperature is dependent on the peripheral and central thermal information sent to the hypothalamus and other areas of the brain. The peripheral thermoreceptors are extremely powerful in driving the initial physiological responses to cold stress. Peripheral vasoconstriction, shivering, and tachycardia are all induced by the cold stimulus. Interestingly, cold receptors adapt to the cold stimuli, thus decreasing their effect on increasing the activity of the somatic and autonomic nervous systems. The range of human response to cold stress suggests that humans have different thresholds for peripheral cold receptor activation. Simplistically, it is thought that various areas of the brain, especially the hypothalamus, compare the peripheral temperatures with the core temperature. By methods still not understood, the CNS is able to activate various responses based on the difference, or the rate of difference, between the periphery and the core. The deleterious effects of mild hypother-

mia on higher brain function (eg, impaired memory, slurred speech) are commonly reported. However, the first response to cold stress is the behavioral one in which the affected person attempts to minimize the cold by altering the immediate environment. Such activities as huddling, walking faster, and attempting to get out of the wind are all manifestations of the attempt by the CNS to maintain core temperature.

In military situations in which personnel cannot escape the cold environment, tents and sleeping bags are the first line of defense after the personnel gear that the subjects wear. In the event of a breakdown of logistics so that personnel cannot sleep, eat, and drink water in a cold environment, the beginnings of secondary hypothermia will soon show their effect. In the battlefield, the signs of hypothermia will be evident in individuals working with computers or other skills requiring fine motor control and good decision-making skills.

A decrease in core temperature will affect every component of a physiological system: neural innervation to the organ, blood flow to the organ, receptors and other chemicals on the surface of the cells that compose the organ, and hormonal control of the cells and the organ itself, which will then affect other organ systems. All physiological systems are affected by a decrease in core temperature, some more so than others.

Once the physiological systems cannot maintain adequate core temperature, various systems begin to shut down. Of all systems, the most important is the cardiovascular, because cold core temperatures will eventually cause asystole or ventricular fibrillation and ultimately death. Many of the effects of the cold on the heart and vasculature and blood would be of only academic interest were it not for the fact that a hypothermic person is capable of being rewarmed and revitalized. Understanding the pathophysiology of hypothermia is key toward maintaining the well-being of a rewarmed cold casualty. Owing to the life-sparing qualities of hypothermia, the focus in many rescue attempts has been on returning the core temperature to normal values. This approach has its pitfalls.

Although rescue attempts usually concern themselves with thermal stability, the key systems that need to be stabilized in a hypothermic state are the same as in a normothermic state: namely, the cardiovascular and the respiratory systems. Even assuming that these systems have been stabilized, the threat of core afterdrop leading to rewarming collapse remains ever present, especially in field situations. The critical importance of rewarming must be addressed simultaneously with stabilizing the pH level.

Although it has not been vigorously studied, the effect of a decrease in either peripheral or core temperature on the immune response is very important in a field situation. Limited studies suggest that cold inhibits many of the immune responses.

In the real world of men and women being involved in field operations, hypothermia is an ever-present nemesis that attacks the weak and weary. Models that predict human cooling curves and hence survivability cannot ethically be tested and therefore can give only crude estimates of time in terms of human survivability. Each branch of the military service will expose its personnel to cold environments that can insidiously lead to hypothermia. The incidence of hypothermia can be minimized only by scrupulous attention to the state of each individual by the officers in charge. In this era in which technology promises mastery over the environment, it is important to be watchful for the breakdown in logistics that would eventually lead to major casualties due to hypothermia.

REFERENCES

1. Golden R St C. Rewarming. In: Pozos RS, Wittmers LE, eds. *The Nature and Treatment of Hypothermia.* Minneapolis, Minn: University of Minnesota; 1983: 195–208.

2. DaVee TS, Reineberg EJ. Extreme hypothermia and ventricular fibrillation. *Ann Emerg Med.* 1980;9:100–107.

3. Pozos RS, Iaizzo PA, Danzl DF, Mills WT. Limits of tolerance to hypothermia. In: Fregly MJ, Blatteis CM, eds. *Handbook of Physiology.* Vol 1. New York, NY: Oxford University Press; 1996.

4. Hodgdon JA, Hesslink RH, Hackney AC, Vickers RR, Hilbert RP. Norwegian military field exercises in the Arctic: Cognitive and physical performance. *Arctic Med Res.* 1991;50:132–136.

5. Medical Operations in Cold Environments; Institute of Naval Medicine. Debriefing of Falkland Island War. Portsmouth, England; 1983. Attended by Pozos RS, Mills WT, Golden R St C.

6. Brengelmann GL. Dilemma of body temperature measurement In: Shiraki K, Youseff MK, eds. *Man in Stressful Environments: Thermal and Work Physiology.* Springfield, Ill: Charles C Thomas; 1987: 5–22.

7. Ducharme MB, Frim J, Bourdon L, Giesbrecht GG. Evaluation of infrared tympanic thermometers during normothermia and hypothermia in humans. *Ann N Y Acad Sci.* 1997;813(Mar):225–229.

8. Sopchick TL, Trone DW, Pozos RS. *Evaluation of Infrared Thermometry of Tympanic Cavity as an Indicator of Core Temperature.* San Diego, Calif: Naval Health Research Center; 1994: 2–15. Technical Report 94-3.

9. Livingstone SD, Grayson J, Frim J, Allen CL, Limmer RE. Effect of cold exposure on various sites of core temperature measurement. *J Appl Physiol.* 1983;54(4):1025–1031.

10. McCaffrey TV, McCook RD, Wourster RD. Effect of head skin temperature on tympanic and oral temperature in man. *J Appl Physiol.* 1975;39(1):114–118.

11. Cooper EE, Kenyon JR. A comparison of temperatures measured on the rectum, oesophagus and on the surface of the aorta during hypothermia in man. *Br J Surg.* 1957;44:616–619.

12. Gerbrandy J, Snell ES, Cranston WI. Oral, rectal and esophageal temperatures in relation to central temperature control in man. *Clin Sci.* 1954;13:615–624.

13. Lilly JK, Boland JP, Zekan S. Urinary bladder temperature monitoring: A new index of body core temperature. *Crit Care Med.* 1980;8(12):742–744.

14. Ralley FE, Ramsay JG, Wanmands JE, Townsend GE, Whalley DG, Delli Colli P. Effect of heated humidified gases on temperature drop after cardiopulmonary bypass. *Anesth Analg.* 1984;63(12):1106–1110.

15. Iggo A. Cutaneous thermoreceptors in primates and sub-primates. *J Physiol (Lond).* 1969;200:403–430.

16. Schafer K, Braun HA, Isenberg C. Effect of menthol on cold receptor activity: Analysis of receptor processes. *J Gen Physiol.* 1986;88:757–776.

17. Iggo A, Young DW. Cutaneous thermoreceptors and thermal nociceptors. In: Kornhuber HH, ed. *The Somatosensory Systems*. Stuttgart, Germany: Thieme; 1975: 5–22.

18. Dawson NJ, Dickenson AH, Hellon RF, Woolf CJ. Inhibitory controls on thermal neurones in the spinal trigeminal nucleus of cats and rats. *Brain Res.* 1981;209(2):440–445.

19. Pierau F-K, Wurster RD, Neya T, Yamasato T, Ulrich J. Generation and processing of peripheral temperature signals in mammals. *Int J Biometeorol.* 1980;24:243–252.

20. Boulant JA, Bignall KE. Hypothalamic neuronal responses to peripheral and deep-body temperatures. *Am J Physiol.* 1973;225:1371–1374.

21. Boulant JA, Hardy JD. The effect of spinal and skin temperatures on the firing rat and thermosensitivity of preoptic neurons. *J Physiol.* 1974;240:639–660.

22. Thompson SM, Masukawa LM, Prince DA. Temperature dependence of intrinsic membrane properties and synaptic potentials in hippocampal CA1 neurons in vitro. *J Neurosci.* 1985;5:817–824.

23. Simon E, Pierau F-K, Taylor DCM. Central and peripheral thermal control of effectors in homeothermic temperature regulation. *Physiol Rev.* 1986;66:235–309.

24. Simon E. Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. *Rev Physiol Biochem Pharmacol.* 1974;71:1–76.

25. Boulant JA, Silva NL. Interactions of reproductive steroids, osmotic pressure and glucose on thermosensitive neurons in preoptic tissue slices. *Can J Physiol Pharmacol.* 1987;65:1267–1273.

26. Boulant JA, Silva NL. Multisensory hypothalamic neurons may explain interactions among regulatory systems. *Newsl Int Physiol Soc.* 1989;4:245–248.

27. Gagge AP, Gonzalez RR. Mechanisms of heat exchange: Biophysics and physiology. In: Fregly MJ, Blatteis CM, eds. *Handbook of Physiology.* Vol 1. New York, NY: Oxford University Press; 1996: 45–84.

28. Brooks VB. Study of brain function by local reversible cooling. *Rev Physiol Biochem Pharmacol.* 1983;95:1–109.

29. Starkov PM, Hammond RE, trans; Neil E, ed. *The Problem of Acute Hypothermia.* New York, NY: Pergamon Press; 1960: 2–31. Russian monograph.

30. Hayward JN, Baker MA. A comparative study of the role of the cerebral blood in the regulation of brain temperature in five mammals. *Brain Res*. 1969;16:417–440.

31. Calvin WH. Generation of spike trains in CNS neurons. *Brain Res*. 1975;84:1–22.

32. Paton BC. Accidental hypothermia. In: Shonbaum E, Lomax P, eds. *Thermoregulation: Pathology, Pharmacology and Therapy*. New York, NY: Pergamon Press; 1991: 397–443.

33. Bering EA Jr. Effects of profound hypothermia and circulatory arrest on cerebral oxygen metabolism and cerebrospinal fluid electrolyte composition in dogs. *J Neurosurg*. 1974;39:199–204.

34. Lanier WL, Iaizzo PA, Murray MJ. The effects of forced-air cooling and rewarming on systemic and central nervous physiology in isoflurane-anesthetized dogs. *Resuscitation*. 1992;23:121–136.

35. Steen PA, Soule EH, Michenfelder JD. Detrimental effect of prolonged hypothermia in cats and monkeys with and without regional cerebral ischemia. *Stroke.* 1979;10:522–529.

36. Krantis A. Hypothermia-induced reduction in the permeation of radio-labelled tracer substances across the blood brain barrier. *Acta Neuropathol (Berl).* 1983;60:61–69.

37. Dietrich WD, Halley M, Valdes I, Bustos R. Interrelationships between increased vascular permeability and acute neuronal damage following temperature controlled brain ischemia in rats. *Acta Neuropathol*. 1991;81:615–625.

38. Dempsey RJ, Combs DJ, Maley ME, Cowen DE, Roy MW, Donaldson DL. Moderate hypothermia reduced post-ischemic edema development and leukotriene production. *Neurosurgery.* 1987;21(2):177–181.

39. Greeley WJ, Ungerleider RM, Smith LR, Reves JG. The effects of deep hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral blood flow in infants and children. *J Thorac Cardiovasc Surg.* 1989;97:737–745.

40. Mizrahi EM, Patel VM, Crawford ES, Coselli JS, Hess KR. Hypothermic-induced electrocerebral silence, prolonged circulatory arrest and cerebral protection during cardiovascular surgery. *Electroencephalogr Clin Neurophysiol.* 1989;72:81–85.

41. Taylor CA. Surgical hypothermia. In: Schonbaum E, Lomax P, eds. *Thermoregulation Pathology, Pharmacology and Therapy*. New York, NY: Pergamon Press; 1991: 363–396.

42. Michenfelder JD, Milde JH. The relationship among canine brain temperature, metabolism, and function during hypothermia. *Anesthesiology.* 1991;75:130–136.

43. Michenfelder JD, Theye RA. The effects on anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. *Anesthesiology.* 1970;33:430–439.

44. Terry HR, Daw EF, Michenfelder JD. Hypothermia by extracorporeal circulation for neurosurgery: An anesthetic technic. *Anesth Analg.* 1962;41:241–248.

45. Leonov Y, Sterz F, Safar P, et al. Mild cerebral hypothermia during and after cardiac arrest improved neurologic outcome in dogs. *J Cereb Blood Flow Metab*. 1990;10:57–70.

46. Iserson KV, Huestis DW. Blood warming: Current applications and techniques. *Transfusion*. 1991;31:558–571.

47. Natale JE, D'Alecy LG. Protection from cerebral ischemia by brain cooling without reduced lactate accumulation in dogs. *Stroke.* 1989;20:770–777.

48. Busto R, Dietrich WD, Mordecai G, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intraischemia brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab*. 1987;7:729–738.

49. Minamisawa H, Smith ML, Siesjo BK. The effect of mild hypothermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. *Ann Neurol*. 1990;28:26–33.

50. Clark RP, Edholm OG. *Man and His Thermal Environment.* London, England: Edward Arnold Publ, Ltd; 1985: 153–158.

51. Petjan JH, Williams DD. Behavior of single motor units during preshivering tone and shivering tremor. *Am J Phys Med*. 1972;51:17–22.

52. Martin S, Cooper KE. Factors which affect shivering in man during cold water immersion. *Pflügers Arch*. 1981;391(1):81–83.

53. Hemmingway A. Shivering. *Physiol Rev*. 1963;43:397–422.

54. Perkins JF Jr. The role of proprioceptors in shivering. *Am J Physiol*. 1945;145:264–271.

55. Iaizzo PA, Wittmers LE, Pozos RS. Shiver of the ankle. *Physiologist*. 1983;26:42–46.

56. Hegnauer AH, D'Amato HD, Flynn J. Influence of intraventricular catheters on the course of immersion hypothermia in the dog. *Am J Physiol*. 1951;167:63–68.

57. Klenow CM. Attenuation of Shiver Amplitude Through Mathematical and Physical Tasks. Duluth, Minn: University of Minnesota Graduate School; 1987. Thesis.

58. Hammel HT, Hardy JD, Fusco MM. Thermoregulatory responses to hypothalamic cooling and unanesthetized dogs. *Am J Physiol*. 1960;198:481–486.

59. Kundt HW, Bruck K, Hensel H. Hypothalamuspenderthur und Haudachelutung des Nichtnarkotisieren Katze. *Arch Gen Physiol.* 1957;264:97–106.

60. Lim TPK. Central and peripheral control mechanism of shivering and its effects on respiration. *J Appl Physiol.* 1960;15:567–574.

61. Pozos RS. Cold stress and its effects on neural junction. In: Lauvsen GA, Pozos RS, Hempel FG, eds. *Human Performance in the Cold*. Bethesda, Md: Undersea Medical Society; 1984: 25–35.

62. Roberts DE, Barr JC, Kerr D, Murray C, Harris R. Fluid replacement during hypothermia. *Aviat Space Environ Med*. 1985;56:333–337.

63. Opstand PK, Erevenger R, Nummestad M, Ruabe N. Performance, mood, and clinical symptoms in men exposed to prolonged, severe, physiological work and sleep deprivation. *Aviat Space Environ Med*. 1978;49:1065–1073.

64. Shapiro CM, Goll CC, Cohen GR, Oswald I. Heat production during sleep. *J Appl Physiol*. 1984;56:671–677.

65. Tafari N, Gentz J. Aspects of rewarming newborn infants with severe accidental hypothermia. *Acta Pediatr Scand*. 1974;63:595–600.

66. MacKenzie MA, Aengevaeren WRM, van der Werf T, Hermus ARMM, Kloppenborg PWC. Effects of steady human poikilothermia. *Arctic Med Res*. 1991;6:67–70.

67. Solomon A, Barish RA, Browne B, Tso E. The electrocardiogram features of hypothermia. *J Emerg Med*. 1989;7:169–173.

68. Preston BR. Effect of hypothermia on systemic and organ system metabolism and function. *J Surg Res.* 1976;20:49–55.

69. MaClean D, Emslie-Smith D. *Accidental Hypothermia*. Philadelphia, Pa: JB Lippincott; 1977: 86–96.

70. Nessmann ME, Busch HM, Gundersen AL. Asystolic cardiac arrest in hypothermia. *Wis Med J*. 1983;82:19–20.

71. Lilly RB Jr. Inadvertent hypothermia: A real problem. In: Bararsh PG, ed. *ASA Refresher Courses in Anesthesiology*. Vol 15. Philadelphia, Pa: JB Lippincott; 1987: 93–107.

72. Fabiato A, Fabiato E. Contraction induced by calcium-triggered release of calcium from sarcoplasmic reticulum of single skinned cardiac cells. *J Physiol*. 1975;249:469–495.

73. Wong KC. Physiology and pharmacology of hypothermia. *West J Med*. 1983;138:227–232.

74. Janse MJ, Al WT. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardiac ischemia and infarction. *Physiol Rev*. 1989;69:1049–1169.

75. Neill WA, Duncan DA, Kloster F, Mohler DJ. Response of the coronary circulation to cutaneous cold. *Ann J Med*. 1974;56:471–476.

76. Ledingham I, Mone JG. Treatment of accidental hypothermia: A prospective clinical study. *Br Med J*. 1980;1:1102–1105.

77. Kiley JP, Eldridge FL, Melhorn DE. Respiration during hypothermia: Effect of rewarming intermediate areas of ventral medulla. *J Appl Physiol*. 1985;59:1423–1427.

78. Johnston CE, Elias DA, Ready AE, Giesbrecht GG. Hypercapnia lowers the shivering threshold and increases core cooling rate in humans. *Aviat Space Environ Med.* 1996;67:438–444.

79. Severinghaus JW. Respiration and hypothermia. *Ann NY Acad Sci.* 1959;80:384–394.

80. Spurr GB, Barlow G. Influence of prolonged hypothermia and hypothermia and hyperthermia on myocardial sodium, potassium and chloride. *Circ Res.* 1959;7:210–218.

81. Conn AW, Barker GA, Edmonds JF, Bohn DJ. Submersion hyperthermia and near drowning. In: Pozos RS, Wittmers LE, eds. *The Nature and Treatment of Hypothermia.* Minneapolis, Minn: University of Minnesota Press; 1983: 152–164.

82. Conn AW. Near drowning and hypothermia. *Can Med Assoc J.* 1979;120:397–400. Editorial.

83. Hamlett M. The fluid shifts in hypothermia. In: Pozos RS, Wittmers LE, eds. *The Nature and Treatment of Hypothermia*. Minneapolis, Minn: University of Minnesota Press; 1983: 94–99.

84. Lennquist MD, Grandberg PO, Bertil W. Fluid balance and physical work capacity in humans exposed to cold. *Arch Environ Health.* 1974;29:241–249.

85. Cupples WA, Fox GR, Hayward JS. Effect of cold water immersion and its combination with alcohol intoxication on urine flow rate of man. *Can J Physiol Pharmacol.* 1980;58:319–321.

86. Ohmura A, Wong KC, Westenskow DR, Shaw CL. Effects of hypocarbia and normocarbia on cardiovascular dynamics and regional circulation in the hypothermic dog. *Anesthesiology*. 1979;50:293–298.

87. Chen RY, Chien S. Plasma volume, red cell volume and thoracic duct lymph flow in hypothermia. *Am J Physiol.* 1977;233(Heart Circ Physiol 4):H605–H612.

88. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet*. 1996;347:289–292.

89. White FN. Reassessing acid–base balance in hypothermia—A comparative point of view. *West J Med.* 1983;138:255–257.

90. Miller JW, Danzl DF, Thomas DM. Urban accidental hypothermia: 135 cases. *Ann Emerg Med.* 1980;9:456–461.

91. Rogenfield JB. Acid–base and electrolyte disturbance in hypothermia. *Am J Cardiol*. 1963;12:678–684.

92. White FN. Temperature and acid–base homeostasis. In: Lauvsen GA, Pozos RS, Hempel FG, eds. *Human Performance in the Cold*. Bethesda, Md: Undersea Medical Society; 1984: 37–50.

93. Rahn H, Reeves RB, Howell BJ. Hydrogen ion regulation, temperature and evolution. *Am Rev Respir Dis*. 1975;112:165–172.

94. Rahn H. Body temperature and acid–base regulation. *Pneumonologie*. 1974;151:87–94.

95. Becker H, Vinten-Johansen J, Buckenberg GD, et al. Myocardial damage caused by keeping pH 7.40 during systemic deep hypothermia. *J Thorac Cardiovasc Surg*. 1981;82:507–515.

96. Swain JA, White FN, Peters RM. The effect of pH on the hypothermia ventricular fibrillation threshold. *J Thorac Cardiovasc Surg*. 1984;87:445–451.

97. Sinet M, Muffat-Joly M, Bendance T, Pocidalo JJ. Maintaining blood pH at 7.4 during hypothermia has no significant effect on work of the isolated rat heart. *Anesthesiology*. 1985;62:582–587.

98. Kroncke GM, Nichols RD, Mendenhall JT, Myerowitz PD, Starling JR. Ectothermic philosophy of acid–base balance to prevent fibrillation during hypothermia. *Arch Surg.* 1986;121:303–304.

99. Harnett RM, Pruitt JR, Sias FR. A review of the literature concerning resuscitation from hypothermia, I: The problem and general approaches. *Aviat Space Environ Med*. 1980;51:680–687.

100. Drake CT, Lewis BJ. The plasma volume expanding effect of low molecular weight dextran in the hypothermic dog. *Surg Forum.* 1961;12:182–187.

101. Danzl DF, Hedges JR, Pozos RS, et al. Hypothermia outcome score: Development and implications. *Crit Care Med*. 1989;17:227–231.

102. Mant AK. Autopsy diagnosis of accidental hypothermia. *J Forensic Sci*. 1969;16:126–129.

103. Bauer RW, Holloway RJ, Krebs JS. The liver in hypothermia. *Ann N Y Acad Sci*. 1959;80:395–450.

104. Therminarias A, Pellerei E. Plasma catecholamines and metabolic changes during cooling and rewarming in dogs. *Exp Biol.* 1987;47:117–123.

105. MaClean D, Browning MC. Plasma 11-hydroxycorticosteroid concentrations and prognosis in accidental hypothermia. *Resuscitation*. 1974;3(4):249–256.

106. Stoner HB, Frayn KD, Little RA, et al. Metabolic aspects of hypothermia in the elderly. *Clin Sci.* 1980;59:19–27.

107. Woolff PD, Hollander CS, Mitsuma T, Lee LA, Loupe A, Schalch DS. Accidental hypothermia: Endocrine functions during recovery. *J Clin Endocrinol Med*. 1972;34:460–466.

108. Prescott LF, Peard MC, Wallace IR. Accidental hypothermia: A common condition. *Br Med J.* 1962;2:1367–1370.

109. Savides EP, Hoffbrand BT. Hypothermia thrombosis and acute pancreatitis. *Br Med J*. 1974;1:614.

110. Haeght JSJ, Keating WR. Failure of thermoregulation in the cold during hypoglycemia induced by exercise and alcohol. *J Physiol*. 1973;229:87–97.

111. Van Oss CJ, Absolau DR, Moore LL, Park BH, Humbert JR. Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and oxygen consumption of human polymorphonuclear leukocytes. *J Reticuloendothel Soc.* 1980;27:561–565.

112. Le Deist F, Menasché P, Kucharski C, Bel A, Piwnica A, Bloch G. Hypothermia during cardiopulmonary bypass delays but does not prevent neutrophil-endothelial cell adhesion: A clinical study. *Circulation*. 1995;92(suppl 9):ii354–ii358.

113. Kluger MJ. Is fever beneficial? *Yale J Biol Med.* 1986;59:89–95.

114. Roberts NJ. Temperature and host defense. *Microbiol Rev.* 1979;43:241–259.

115. Park MM, Hornback NB, Endres S, Dinarello CA. The effect of whole body hyperthermia on the immune cell activity of cancer patients. *Lymphokine Res.* 1990;9:213–223.

116. Sessler DI, Israel D, Pozos RS, Pozos M, Rubenstein EH. Spontaneous post-anesthetic tremor does not resemble thermoregulatory shivering. *Anesthesiology*. 1988;68:843–850.

117. Webb P. Temperatures of skin, subcutaneous tissue, muscle and core in resting men in cold, comfortable and hot conditions. *Eur J Appl Physiol*. 1992;64:471–476.

118. Swan H, Zearin I, Holmes JH, Montgomery V. Cessation of circulation in general hypothermia, I: Physiological changes and their control. *Ann Surg.* 1953;138:360–376.

119. Rodbard DH, Rodbard W, Rodbard S. Temperature: A critical factor determining localization and natural history of infectious, metabolic and immunological diseases. *Perspect Biol Med*. 1980;23:439–474.

120. Biggar WD, Bohn DJ, Kent G. Neutrophil migration in vitro and in vivo during hypothermia. *Infect Immun*. 1983;46:857–859.

121. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med.* 1996;334:1209–1215.

122. Wang-Yang MC, Buttke TM, Miller NW, Clem LW. Temperature-mediated processes in immunity: Differential effects of low temperature on mouse T helper cell responses. *Cell Immunol.* 1990;126:354–366.

123. Abbas AK, Lichtman AH, Pober JS. *Cellular and Molecular Immunology*. Philadelphia, Pa: WB Saunders, Harcourt Brace Jovanovich; 1991: 396.

124. Sundaresan G, Suthanthirarajan N, Namasivayam A. Certain immunological parameters in subacute cold stress. *Indian J Physiol Pharmacol.* 1990;34:57–60.

125. Cheng GJ, Morrow-Tesch JL, Beller DI, Levy EM, Black PH. Immunosuppression in mice induced by cold water stress. *Brain Behav Immun*. 1990;4:278–291.

126. Aarstad H, Thiele D, Seljelis R. The effect of various contexts of stress on the mouse spleen lymphocytes and macrophage co-stimulatory activity. *Scand J Immunol*. 1991;33:461–472.

127. Rodbard D. The role of regional body temperature in the pathogenesis of disease. *N Engl J Med*. 1981;305:808–814.

128. Endrich B, Hammersen F, Messmer K. Microvascular ultrastructure in non-freezing cold injuries. *Res Exp Med (Berl)*. 1990;190:365–379.

129. Kizaki T, Ookawara T, Izawa T, et al. Relationship between cold tolerance and generation of suppressor macrophages during acute cold stress. *J Appl Physiol.* 1997;83(4):1116–1122.

130. Mills WJ Jr. Personal communication, 1973.

131. Giesbrecht G, Sessler GDI, Mekjavic I, Schroeder M, Bristow GK. Treatment of mild immersion hypothermia by direct body-to-body contact. *J Appl Physiol*. 1994;76(6):2373–2379.

132. Boundary Waters Committee on Safety. *Standard Practice for Rewarming Mild Hypothermic Victims in Boundary Waters Canoe Area—Minnesota.* Minneapolis, Minn: Boundary Waters Committee on Safety; 1979.

133. Golden GSC, Hervey GR. The mechanism of the after-drop following immersion hypothermia in pigs. *J Physiol*. 1977;272:26–27.

134. Hoskin RW, Melinyshyn MJ, Romet TT, Goode RC. Bath rewarming from immersion hypothermia. *J Appl Physiol.* 1986;73:1253–1258.

135. Young A. Homeostatic responses to prolonged cold exposure: Human cold adaptation. In: Fregly MJ, Blatteis CM, eds. *Handbook of Physiology.* Vol 1. New York, NY: Oxford University Press; 1996: 419–437.