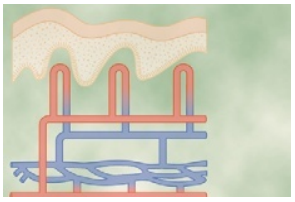
Body Temperature Regulation, and Fever



Normal Body Temperatures

Body Core Temperature and Skin Temperature. The temperature of the deep tissues of the body—the "core" of the body—remains very constant, within ±1°F (±0.6°C), except when a person develops a febrile illness. Indeed, a nude person can be exposed to temperatures as low as 55°F or as high as 130°F in *dry* air and still maintain an almost constant core temperature. The mechanisms for regulating body temperature represent a beautifully designed control system. In this chapter we discuss this system as it operates in health and in disease.

The *skin temperature*, in contrast to the *core temperature*, rises and falls with the temperature of the surroundings. The skin temperature is important when we refer to the skin's ability to lose heat to the surroundings.

Normal Core Temperature. No single core temperature can be considered normal because measurements in many healthy people have shown a *range* of normal temperatures measured orally, as shown in Figure 73-1, from less than 97°F (36°C) to over 99.5°F (37.5°C). The average normal core temperature is generally considered to be between 98.0° and 98.6°F when measured orally and about 1°F higher when measured rectally.

The body temperature increases during exercise and varies with temperature extremes of the surroundings because the temperature regulatory mechanisms are not perfect. When excessive heat is produced in the body by strenuous exercise, the temperature can rise temporarily to as high as 101°F to 104°F. Conversely, when the body is exposed to extreme cold, the temperature can fall below 96°F.

Body Temperature Is Controlled by Balancing Heat Production and Heat Loss

When the rate of heat production in the body is greater than the rate at which heat is being lost, heat builds up in the body and the body temperature rises. Conversely, when heat loss is greater, both body heat and body temperature decrease. Most of the remainder of this chapter is concerned with this balance between heat production and heat loss and the mechanisms by which the body controls each of these.

Heat Production

Heat production is a principal by-product of metabolism. In Chapter 72, which summarizes body energetics, we discuss the different factors that determine the rate of heat production, called the *metabolic rate of the body*. The most important of these factors are listed again here: (1) basal rate of metabolism of all the cells of the body; (2) extra rate of metabolism caused by muscle activity, including muscle contractions caused by shivering; (3) extra metabolism caused by the effect of thyroxine (and, to a less extent, other hormones, such as growth hormone and testosterone) on the cells; (4) extra metabolism caused by the effect of epinephrine, norepinephrine, and sympathetic stimulation on the cells; (5) extra metabolism caused by increased chemical activity in the cells themselves, especially when the cell temperature increases; and (6) extra metabolism needed for digestion, absorption, and storage of food (thermogenic effect of food).

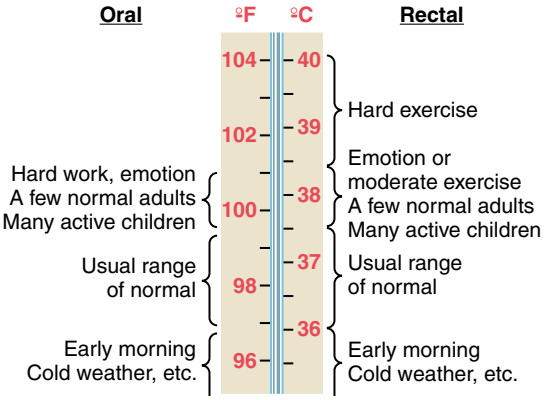


Figure 73-1 Estimated range of body "core" temperature in normal people. (Redrawn from DuBois EF: Fever. Springfield, Ill: Charles C Thomas, 1948.)

Heat Loss

Most of the heat produced in the body is generated in the deep organs, especially in the liver, brain, and heart, and in the skeletal muscles during exercise. Then this heat is transferred from the deeper organs and tissues to the skin, where it is lost to the air and other surroundings. Therefore, the rate at which heat is lost is determined almost entirely by two factors: (1) how rapidly heat can be conducted from where it is produced in the body core to the skin and (2) how rapidly heat can then be transferred from the skin to the surroundings. Let us begin by discussing the system that insulates the core from the skin surface.

Insulator System of the Body

The skin, the subcutaneous tissues, and especially the fat of the subcutaneous tissues act together as a heat insulator for the body. The fat is important because it conducts heat only *one third* as readily as other tissues. When no blood is flowing from the heated internal organs to the skin, the insulating properties of the normal male body are about equal to three-quarters the insulating properties of a usual suit of clothes. In women, this insulation is even better.

The insulation beneath the skin is an effective means of maintaining normal internal core temperature, even though it allows the temperature of the skin to approach the temperature of the surroundings.

Blood Flow to the Skin from the Body Core Provides Heat Transfer

Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries, shown in Figure 73-2. In the most exposed areas of the body—the hands, feet, and ears—blood is also supplied to the plexus directly from the small arteries through highly muscular *arteriovenous anastomoses*.

The rate of blood flow into the skin venous plexus can vary tremendously—from barely above zero to as great as 30 percent of the total cardiac output. A high rate of skin flow causes heat to be conducted from the core of the body to the skin with great efficiency, whereas reduction in the rate of skin flow can decrease the heat conduction from the core to very little.

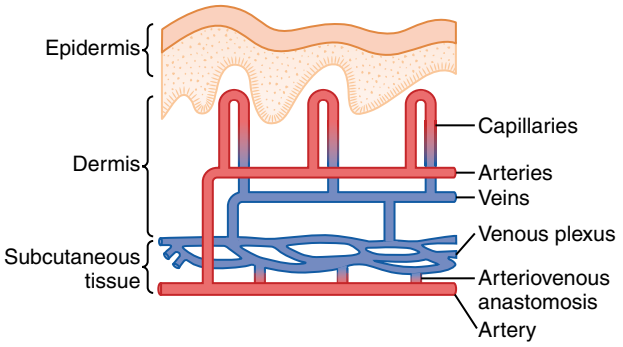


Figure 73-2 Skin circulation.

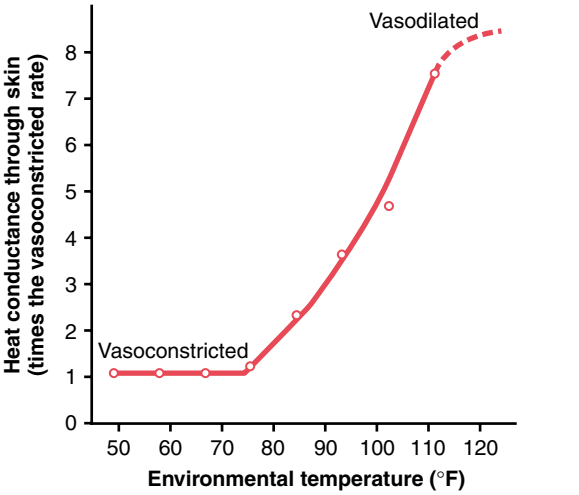


Figure 73-3 Effect of changes in the environmental temperature on heat conductance from the body core to the skin surface. (Modified from Benzinger TH: Heat and Temperature Fundamentals of Medical Physiology. New York: Dowden, Hutchinson & Ross, 1980.)

Figure 73-3 shows quantitatively the effect of environmental air temperature on conductance of heat from the core to the skin surface and then conductance into the air, demonstrating an approximate eightfold increase in heat conductance between the fully vasoconstricted state and the fully vasodilated state.

Therefore, the skin is an effective *controlled "heat radiator" system*, and the flow of blood to the skin is a most effective mechanism for heat transfer from the body core to the skin.

Control of Heat Conduction to the Skin by the Sympathetic Nervous System. Heat conduction to the skin by the blood is controlled by the degree of vasoconstriction of the arterioles and the arteriovenous anastomoses that supply blood to the venous plexus of the skin. This vasoconstriction is controlled almost entirely by the sympathetic nervous system in response to changes in body core temperature and changes in environmental temperature. This is discussed later in the chapter in connection with control of body temperature by the hypothalamus.

Basic Physics of How Heat Is Lost from the Skin Surface

The various methods by which heat is lost from the skin to the surroundings are shown in Figure 73-4. They include *radiation, conduction*, and *evaporation*, which are explained next.

Radiation. As shown in Figure 73-4, in a nude person sitting inside at normal room temperature, about 60 percent of total heat loss is by radiation.

Loss of heat by radiation means loss in the form of infrared heat rays, a type of electromagnetic wave. Most infrared heat rays that radiate from the body have wavelengths of 5 to 20 micrometers, 10 to 30 times the wavelengths of light rays. All objects that are not at absolute zero temperature radiate such rays. The human body

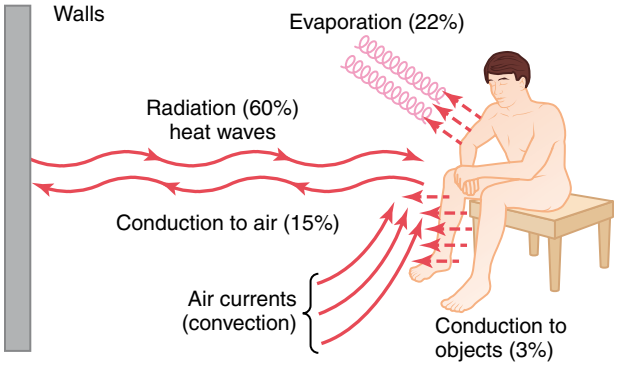


Figure 73-4 Mechanisms of heat loss from the body.

radiates heat rays in all directions. Heat rays are also being radiated from the walls of rooms and other objects toward the body. If the temperature of the body is greater than the temperature of the surroundings, a greater quantity of heat is radiated from the body than is radiated to the body.

Conduction. As shown in Figure 73-4, only minute quantities of heat, about 3 percent, are normally lost from the body by direct conduction from the surface of the body to *solid objects*, such as a chair or a bed. Loss of heat by *conduction to air*, however, represents a sizable proportion of the body's heat loss (about 15 percent) even under normal conditions.

It will be recalled that heat is actually the kinetic energy of molecular motion, and the molecules of the skin are continually undergoing vibratory motion. Much of the energy of this motion can be transferred to the air if the air is colder than the skin, thus increasing the velocity of the air molecules' motion. Once the temperature of the air adjacent to the skin equals the temperature of the skin, no further loss of heat occurs in this way because now an equal amount of heat is conducted from the air to the body. Therefore, conduction of heat from the body to the air is self-limited *unless the heated air moves away from the skin*, so new, unheated air is continually brought in contact with the skin, a phenomenon called *air convection*.

Convection. The removal of heat from the body by convection air currents is commonly called *heat loss by convection*. Actually, the heat must first be *conducted* to the air and then carried away by the convection air currents.

A small amount of convection almost always occurs around the body because of the tendency for air adjacent to the skin to rise as it becomes heated. Therefore, in a nude person seated in a comfortable room without gross air movement, about 15 percent of his or her total heat loss occurs by conduction to the air and then by air convection away from the body.

Cooling Effect of Wind. When the body is exposed to wind, the layer of air immediately adjacent to the skin is replaced by new air much more rapidly than normally, and heat loss by convection increases accordingly. The cooling effect of wind at low velocities is about proportional to the *square root of the wind velocity*. For instance, a wind of 4 miles per hour is about twice as effective for cooling as a wind of 1 mile per hour.

Conduction and Convection of Heat from a Person Suspended in Water. Water has a specific heat several thousand times as great as that of air, so each unit portion of water adjacent to the skin can absorb far greater quantities of heat than air can. Also, heat conductivity in water is very great in comparison with that in air. Consequently, it is impossible for the body to heat a thin layer of water next to the body to form an "insulator zone" as occurs in air. Therefore, the rate of heat loss to water is usually many times greater than the rate of heat loss to air.

Evaporation. When water evaporates from the body surface, 0.58 Calorie (kilocalorie) of heat is lost for each gram of water that evaporates. Even when a person is not sweating, water still evaporates *insensibly* from the skin and lungs at a rate of about 600 to 700 ml/day. This causes continual heat loss at a rate of 16 to 19 Calories per hour. This insensible evaporation through the skin and lungs cannot be controlled for purposes of temperature regulation because it results from continual diffusion of water molecules through the skin and respiratory surfaces. However, loss of heat by *evaporation of sweat* can be controlled by regulating the rate of sweating, which is discussed later in the chapter.

Evaporation Is a Necessary Cooling Mechanism at Very High Air Temperatures. As long as skin temperature is greater than the temperature of the surroundings, heat can be lost by radiation and conduction. But when the temperature of the surroundings becomes greater than that of the skin, instead of losing heat, the body gains heat by both radiation and conduction. Under these conditions, *the only means by which the body can rid itself of heat is by evaporation*.

Therefore, anything that prevents adequate evaporation when the surrounding temperature is higher than the skin temperature will cause the internal body temperature to rise. This occurs occasionally in human beings who are born with congenital absence of sweat glands. These people can tolerate cold temperatures as well as normal people can, but they are likely to die of heatstroke in tropical zones because without the evaporative refrigeration system, they cannot prevent a rise in body temperature when the air temperature is above that of the body.

Effect of Clothing on Conductive Heat Loss. Clothing entraps air next to the skin in the weave of the cloth, thereby increasing the thickness of the so-called *private zone* of air adjacent to the skin and also decreasing the flow of convection air currents. Consequently, the rate of heat loss from the body by conduction and convection is greatly depressed. A usual suit of clothes decreases the rate of heat loss to about half that from the nude body, but arctic-type clothing can decrease this heat loss to as little as one sixth.

About half the heat transmitted from the skin to the clothing is radiated to the clothing instead of being conducted across the small intervening space. Therefore, coating the inside of clothing with a thin layer of gold,

which reflects radiant heat back to the body, makes the insulating properties of clothing far more effective than otherwise. Using this technique, clothing for use in the arctic can be decreased in weight by about half.

The effectiveness of clothing in maintaining body temperature is almost completely lost when the clothing becomes wet because the high conductivity of water increases the rate of heat transmission through cloth 20-fold or more. Therefore, one of the most important factors for protecting the body against cold in arctic regions is extreme caution against allowing the clothing to become wet. Indeed, one must be careful not to become overheated even temporarily because sweating in one's clothes makes them much less effective thereafter as an insulator.

Sweating and Its Regulation by the Autonomic Nervous System

Stimulation of the anterior hypothalamus-preoptic area in the brain either electrically or by excess heat causes sweating. The nerve impulses from this area that cause sweating are transmitted in the autonomic pathways to the spinal cord and then through sympathetic outflow to the skin everywhere in the body.

It should be recalled from the discussion of the autonomic nervous system in Chapter 60 that the sweat glands are innervated by *cholinergic* nerve fibers (fibers that secrete acetylcholine but that run in the sympathetic nerves along with the adrenergic fibers). These glands can also be stimulated to some extent by epinephrine or norepinephrine circulating in the blood, even though the glands themselves do not have adrenergic innervation. This is important during exercise, when these hormones are secreted by the adrenal medullae and the body needs to lose excessive amounts of heat produced by the active muscles.

Mechanism of Sweat Secretion. In Figure 73-5, the sweat gland is shown to be a tubular structure consisting of two parts: (1) a deep subdermal *coiled portion* that secretes the sweat, and (2) a *duct portion* that passes outward through the dermis and epidermis of the skin. As is true of so many other glands, the secretory portion of the sweat gland secretes a fluid called the *primary secretion* or *precursor secretion*; the concentrations of constituents in the fluid are then modified as the fluid flows through the duct.

The precursor secretion is an active secretory product of the epithelial cells lining the coiled portion of the sweat gland. Cholinergic sympathetic nerve fibers ending on or near the glandular cells elicit the secretion.

The composition of the precursor secretion is similar to that of plasma, except that it does not contain plasma proteins. The concentration of sodium is about 142 mEq/L and that of chloride is about 104 mEq/L, with much smaller concentrations of the other solutes of plasma. As this precursor solution flows through the duct portion of the gland, it is modified by reabsorption of most of the sodium and chloride ions. The degree of this reabsorption depends on the rate of sweating, as follows.

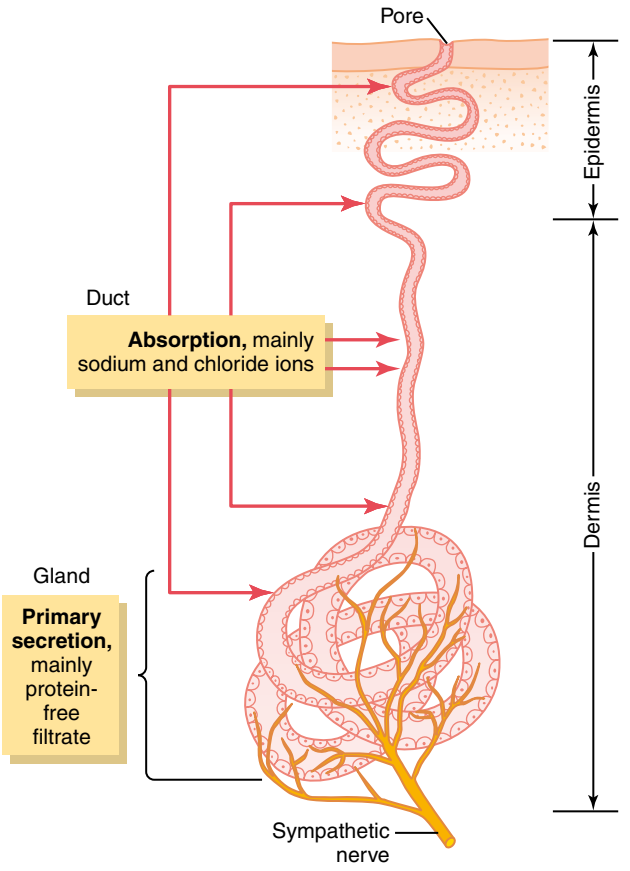


Figure 73-5 Sweat gland innervated by an acetylcholine-secreting sympathetic nerve. A *primary protein-free secretion* is formed by the glandular portion, but most of the electrolytes are reabsorbed in the duct, leaving a dilute, watery secretion.

When the sweat glands are stimulated only slightly, the precursor fluid passes through the duct slowly. In this instance, essentially all the sodium and chloride ions are reabsorbed, and the concentration of each falls to as low as 5 mEq/L. This reduces the osmotic pressure of the sweat fluid to such a low level that most of the water is also reabsorbed, which concentrates most of the other constituents. Therefore, at low rates of sweating, such constituents as urea, lactic acid, and potassium ions are usually very concentrated.

Conversely, when the sweat glands are strongly stimulated by the sympathetic nervous system, large amounts of precursor secretion are formed, and the duct may reabsorb only slightly more than half the sodium chloride; the concentrations of sodium and chloride ions are then (in an *unacclimatized* person) a maximum of about 50 to 60 mEq/L, slightly less than half the concentrations in plasma. Furthermore, the sweat flows through the glandular tubules so rapidly that little of the water is reabsorbed. Therefore, the other dissolved constituents of sweat are only moderately increased in concentration—urea is about twice that in the plasma, lactic acid about 4 times, and potassium about 1.2 times.

There is a significant loss of sodium chloride in the sweat when a person is unacclimatized to heat. There is much

less electrolyte loss, despite increased sweating capacity, once a person has become acclimatized, as follows.

Acclimatization of the Sweating Mechanism to Heat—Role of Aldosterone. Although a normal, unacclimatized person seldom produces more than about 1 liter of sweat per hour, when this person is exposed to hot weather for 1 to 6 weeks, he or she begins to sweat more profusely, often increasing maximum sweat production to as much as 2 to 3 L/hour. Evaporation of this much sweat can remove heat from the body at a rate *more than 10 times* the normal basal rate of heat production. This increased effectiveness of the sweating mechanism is caused by a change in the internal sweat gland cells themselves to increase their sweating capability.

Also associated with acclimatization is a further decrease in the concentration of sodium chloride in the sweat, which allows progressively better conservation of body salt. Most of this effect is caused by *increased secretion of aldosterone* by the adrenocortical glands, which results from a slight decrease in sodium chloride concentration in the extracellular fluid and plasma. An *unacclimatized* person who sweats profusely often loses 15 to 30 grams of salt each day for the first few days. After 4 to 6 weeks of acclimatization, the loss is usually 3 to 5 g/day.

Loss of Heat by Panting

Many lower animals have little ability to lose heat from the surfaces of their bodies, for two reasons: (1) the surfaces are often covered with fur, and (2) the skin of most lower animals is not supplied with sweat glands, which prevents most of the evaporative loss of heat from the skin. A substitute mechanism, the *panting* mechanism, is used by many lower animals as a means of dissipating heat.

The phenomenon of panting is "turned on" by the thermoregulator centers of the brain. That is, when the blood becomes overheated, the hypothalamus initiates neurogenic signals to decrease the body temperature. One of these signals initiates panting. The actual panting process is controlled by a *panting center* that is associated with the pneumotaxic respiratory center located in the pons.

When an animal pants, it breathes in and out rapidly, so large quantities of new air from the exterior come in contact with the upper portions of the respiratory passages; this cools the blood in the respiratory passage mucosa as a result of water evaporation from the mucosal surfaces, especially evaporation of saliva from the tongue. Yet panting does not increase the alveolar ventilation more than is required for proper control of the blood gases because each breath is extremely shallow; therefore, most of the air that enters the alveoli is dead-space air mainly from the trachea and not from the atmosphere.

Regulation of Body Temperature—Role of the Hypothalamus

Figure 73-6 shows what happens to the body "core" temperature of a nude person after a few hours' exposure to *dry* air ranging from 30° to 160°F. The precise dimensions of this curve depend on the wind movement of the air, the amount of moisture in the air, and even the nature of the surroundings. In general, a nude person in dry air between 55° and 130° F is capable of maintaining a normal body core temperature somewhere between 97° and 100°F.

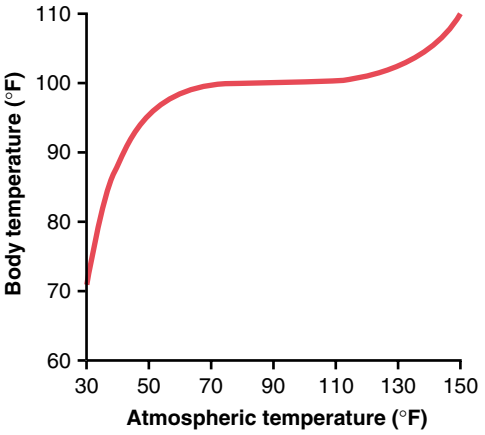


Figure 73-6 Effect of high and low atmospheric temperatures of several hours' duration, under dry conditions, on the internal body "core" temperature. Note that the internal body temperature remains stable despite wide changes in atmospheric temperature.

The temperature of the body is regulated almost entirely by nervous feedback mechanisms, and almost all these operate through *temperature-regulating centers* located in the *hypothalamus*. For these feedback mechanisms to operate, there must also be temperature detectors to determine when the body temperature becomes either too high or too low.

Role of the Anterior Hypothalamic-Preoptic Area in Thermostatic Detection of Temperature

Experiments have been performed in which minute areas in the brain of an animal have been either heated or cooled by use of a *thermode*. This small, needle-like device is heated by electrical means or by passing hot water through it, or it is cooled by cold water. The principal areas in the brain where heat or cold from a thermode affects body temperature control are the preoptic and anterior hypothalamic nuclei of the hypothalamus.

Using the thermode, the anterior hypothalamic-preoptic area has been found to contain large numbers of heat-sensitive neurons, as well as about one-third as many cold-sensitive neurons. These neurons are believed to function as temperature sensors for controlling body temperature. The heat-sensitive neurons increase their firing rate 2- to 10-fold in response to a 10°C increase in body temperature. The cold-sensitive neurons, by contrast, increase their firing rate when the body temperature falls.

When the preoptic area is heated, the skin all over the body immediately breaks out in a profuse sweat, whereas the skin blood vessels over the entire body become greatly dilated. This is an immediate reaction to cause the body to lose heat, thereby helping to return the body temperature toward the normal level. In addition, any excess body heat production is inhibited. Therefore, it is clear that the hypothalamic-preoptic area has the capability to serve as a thermostatic body temperature control center.

Detection of Temperature by Receptors in the Skin and Deep Body Tissues

Although the signals generated by the temperature receptors of the hypothalamus are extremely powerful in controlling body temperature, receptors in other parts of the body play additional roles in temperature regulation. This is especially true of temperature receptors in the skin and in a few specific deep tissues of the body.

It will be recalled from the discussion of sensory receptors in Chapter 48 that the skin is endowed with both *cold* and *warmth* receptors. There are far more cold receptors than warmth receptors—in fact, 10 times as many in many parts of the skin. Therefore, peripheral detection of temperature mainly concerns detecting cool and cold instead of warm temperatures.

When the skin is chilled over the entire body, immediate reflex effects are invoked and begin to increase the temperature of the body in several ways: (1) by providing a strong stimulus to cause shivering, with a resultant increase in the rate of body heat production; (2) by inhibiting the process of sweating, if this is already occurring; and (3) by promoting skin vasoconstriction to diminish loss of body heat from the skin.

Deep body temperature receptors are found mainly in the *spinal cord*, in the *abdominal viscera*, and in or around the *great veins* in the upper abdomen and thorax. These deep receptors function differently from the skin receptors because they are exposed to the body core temperature rather than the body surface temperature. Yet, like the skin temperature receptors, they detect mainly cold rather than warmth. It is probable that both the skin and the deep body receptors are concerned with preventing *hypothermia*—that is, preventing low body temperature.

Posterior Hypothalamus Integrates the Central and Peripheral Temperature Sensory Signals

Even though many temperature sensory signals arise in peripheral receptors, these signals contribute to body temperature control mainly through the hypothalamus. The area of the hypothalamus that they stimulate is located bilaterally in the posterior hypothalamus approximately at the level of the mammillary bodies. The temperature sensory signals from the anterior hypothalamic-preoptic area are also transmitted into this posterior hypothalamic area. Here the signals from the preoptic area and the signals from elsewhere in the body are combined and integrated to control the heat-producing and heat-conserving reactions of the body.

Neuronal Effector Mechanisms That Decrease or Increase Body Temperature

When the hypothalamic temperature centers detect that the body temperature is either too high or too low, they institute appropriate temperature-decreasing or temperature-increasing procedures. The reader is probably familiar with most of these from personal experience, but special features are the following.

Temperature-Decreasing Mechanisms When the Body Is Too Hot

The temperature control system uses three important mechanisms to reduce body heat when the body temperature becomes too great:

1. *Vasodilation of skin blood vessels.* In almost all areas of the body, the skin blood vessels become intensely dilated. This is caused by inhibition of the sympathetic centers in the posterior hypothalamus that cause vasoconstriction. Full vasodilation can increase the rate of heat transfer to the skin as much as eightfold.
2. *Sweating.* The effect of increased body temperature to cause sweating is demonstrated by the blue curve in Figure 73-7, which shows a sharp increase in the rate of evaporative heat loss resulting from sweating when the body core temperature rises above the critical level of 37°C (98.6°F). An additional 1°C increase in body temperature causes enough sweating to remove 10 times the basal rate of body heat production.
3. *Decrease in heat production.* The mechanisms that cause excess heat production, such as shivering and chemical thermogenesis, are strongly inhibited.

Temperature-Increasing Mechanisms When the Body Is Too Cold

When the body is too cold, the temperature control system institutes exactly opposite procedures. They are:

1. *Skin vasoconstriction throughout the body.* This is caused by stimulation of the posterior hypothalamic sympathetic centers.
2. *Piloerection.* Piloerection means hairs "standing on end." Sympathetic stimulation causes the arrector pili

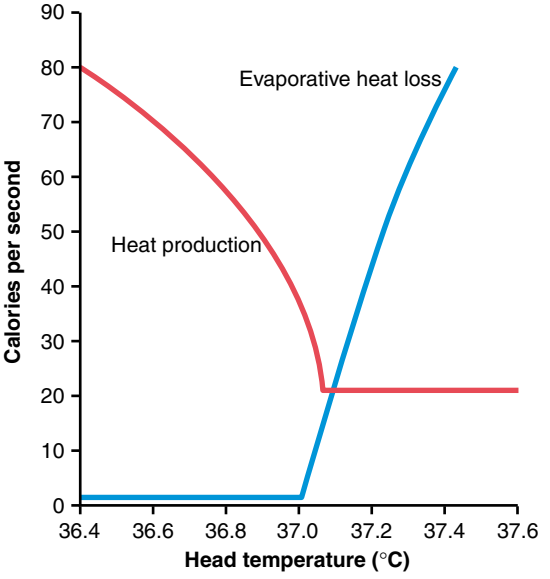


Figure 73-7 Effect of hypothalamic temperature on evaporative heat loss from the body and on heat production caused primarily by muscle activity and shivering. This figure demonstrates the extremely critical temperature level at which increased heat loss begins and heat production reaches a minimum stable level.

muscles attached to the hair follicles to contract, which brings the hairs to an upright stance. This is not important in human beings, but in lower animals, upright projection of the hairs allows them to entrap a thick layer of "insulator air" next to the skin, so transfer of heat to the surroundings is greatly depressed.

3. *Increase in thermogenesis (heat production).* Heat production by the metabolic systems is increased by promoting shivering, sympathetic excitation of heat production, and thyroxine secretion. These methods of increasing heat require additional explanation, which follows.

Hypothalamic Stimulation of Shivering. Located in the dorsomedial portion of the posterior hypothalamus near the wall of the third ventricle is an area called the *primary motor center for shivering*. This area is normally inhibited by signals from the heat center in the anterior hypothalamic-preoptic area but is excited by cold signals from the skin and spinal cord. Therefore, as shown by the sudden increase in "heat production" (see the red curve in Figure 73-7), this center becomes activated when the body temperature falls even a fraction of a degree below a critical temperature level. It then transmits signals that cause shivering through bilateral tracts down the brain stem, into the lateral columns of the spinal cord, and finally to the anterior motor neurons. These signals are nonrhythmical and do not cause the actual muscle shaking. Instead, they increase the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior motor neurons. When the tone rises above a certain critical level, shivering begins. This probably results from feedback oscillation of the muscle spindle stretch reflex mechanism, which is discussed in Chapter 54. *During maximum shivering, body heat production can rise to four to five times normal.*

Sympathetic "Chemical" Excitation of Heat Production. As pointed out in Chapter 72, an increase in either sympathetic stimulation or circulating norepinephrine and epinephrine in the blood can cause an immediate increase in the rate of cellular metabolism. This effect is called *chemical thermogenesis*, or *nonshivering thermogenesis*. It results at least partially from the ability of norepinephrine and epinephrine to *uncouple* oxidative phosphorylation, which means that excess foodstuffs are oxidized and thereby release energy in the form of heat but do not cause ATP to be formed.

The degree of chemical thermogenesis that occurs in an animal is almost directly proportional to the amount of *brown fat* in the animal's tissues. This is a type of fat that contains large numbers of special mitochondria where uncoupled oxidation occurs, as described in Chapter 72. Brown fat is richly supplied with sympathetic nerves that release norepinephrine, which stimulates tissue expression of *mitochondrial uncoupling protein* (also called *thermogenin*) and increases thermogenesis.

Acclimatization greatly affects the intensity of chemical thermogenesis; some animals, such as rats, that have been exposed to a cold environment for several weeks exhibit a 100 to 500 percent increase in heat production when acutely exposed to cold, in contrast to the unacclimatized animal, which responds with an increase of perhaps one third as much. This increased thermogenesis also leads to a corresponding increase in food intake.

In adult human beings, who have almost no brown fat, it is rare for chemical thermogenesis to increase the rate of heat production more than 10 to 15 percent. However, in infants, who *do* have a small amount of brown fat in the interscapular space, chemical thermogenesis can increase the rate of heat production 100 percent, which is probably an important factor in maintaining normal body temperature in neonates.

Increased Thyroxine Output as a Long-Term Cause of Increased Heat Production. Cooling the anterior hypothalamic-preoptic area also increases production of the neurosecretory hormone *thyrotropin-releasing hormone* by the hypothalamus. This hormone is carried by way of the hypothalamic portal veins to the anterior pituitary gland, where it stimulates secretion of *thyroid-stimulating hormone*.

Thyroid-stimulating hormone in turn stimulates increased output of *thyroxine* by the thyroid gland, as explained in Chapter 76. The increased thyroxine activates uncoupling protein and increases the rate of cellular metabolism throughout the body, which is yet another mechanism of *chemical thermogenesis*. This increase in metabolism does not occur immediately but requires several weeks' exposure to cold to make the thyroid gland hypertrophy and reach its new level of thyroxine secretion.

Exposure of animals to extreme cold for several weeks can cause their thyroid glands to increase in size 20 to 40 percent. However, human beings seldom allow themselves to be exposed to the same degree of cold as that to which animals are often subjected. Therefore, we still do not know, quantitatively, how important the thyroid mechanism of adaptation to cold is in the human being.

Isolated measurements have shown that military personnel residing for several months in the arctic develop increased metabolic rates; some Inuit (Eskimos) also have abnormally high basal metabolic rates. Further, the continuous stimulatory effect of cold on the thyroid gland may explain the much higher incidence of toxic thyroid goiters in people who live in cold climates than in those who live in warm climates.

Concept of a "Set-Point" for Temperature Control

In the example of Figure 73-7, it is clear that at a critical body core temperature of about 37.1°C (98.8°F), drastic changes occur in the rates of both heat loss and heat production. At temperatures above this level, the rate of heat loss is greater than that of heat production, so the body temperature falls and approaches the 37.1°C level. At temperatures below this level, the rate of heat production is greater than that of heat loss, so the body temperature

rises and again approaches the 37.1°C level. This crucial temperature level is called the "set-point" of the temperature control mechanism. That is, all the temperature control mechanisms continually attempt to bring the body temperature back to this set-point level.

Feedback Gain for Body Temperature Control. Let us recall the discussion of feedback gain of control systems presented in Chapter 1. Feedback gain is a measure of the effectiveness of a control system. In the case of body temperature control, it is important for the internal core temperature to change as little as possible, even though the environmental temperature might change greatly from day to day or even hour to hour. The *feedback gain* of the temperature control system is equal to the ratio of the change in environmental temperature to the change in body core temperature minus 1.0 (see Chapter 1 for this formula). Experiments have shown that the body temperature of humans changes about 1°C for each 25° to 30°C change in environmental temperature. Therefore, the feedback gain of the total mechanism for body temperature control averages about 27 (28/1.0 – 1.0 = 27), which is an extremely high gain for a biological control system (the baroreceptor arterial pressure control system, by comparison, has a feedback gain of <2).

Skin Temperature Can Slightly Alter the Set-Point for Core Temperature Control

The critical temperature set-point in the hypothalamus above which sweating begins and below which shivering begins is determined mainly by the degree of activity of the heat temperature receptors in the anterior hypothalamic-preoptic area. However, temperature signals from the peripheral areas of the body, especially from the skin and certain deep body tissues (spinal cord and abdominal viscera), also contribute slightly to body temperature regulation. But how do they contribute? The answer is that they alter the set-point of the hypothalamic temperature control center. This effect is shown in Figures 73-8 and 73-9.

Figure 73-8 demonstrates the effect of different skin temperatures on the set-point for sweating, showing that the set-point increases as the skin temperature decreases. Thus, for the person represented in this figure, the hypothalamic set-point increased from 36.7°C when the skin temperature was higher than 33°C to a set-point of 37.4°C when the skin temperature had fallen to 29°C. Therefore, when the skin temperature was high, sweating began at a lower hypothalamic temperature than when the skin temperature was low. One can readily understand the value of such a system because it is important that sweating be inhibited when the skin temperature is low; otherwise, the combined effect of low skin temperature and sweating could cause far too much loss of body heat.

A similar effect occurs in shivering, as shown in Figure 73-9. That is, when the skin becomes cold, it drives the

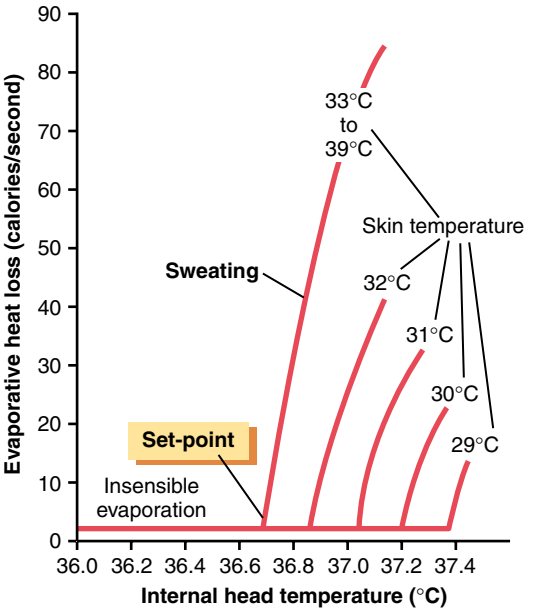


Figure 73-8 Effect of changes in the internal head temperature on the rate of evaporative heat loss from the body. Note that the skin temperature determines the set-point level at which sweating begins. (Courtesy Dr. T. H. Benzinger.)

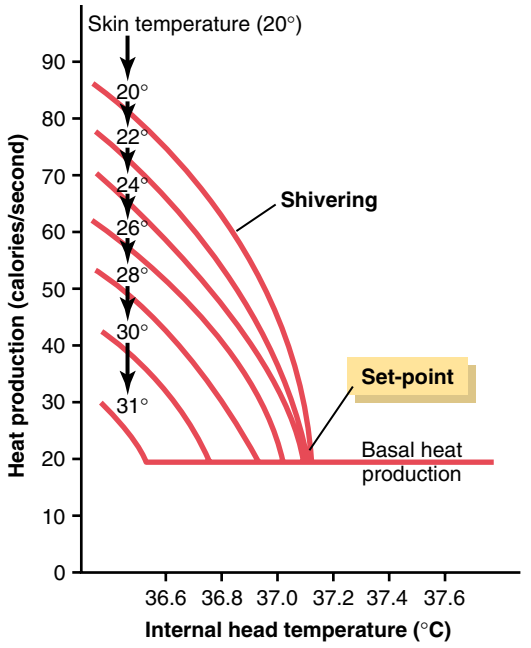


Figure 73-9 Effect of changes in the internal head temperature on the rate of heat production by the body. Note that the skin temperature determines the set-point level at which shivering begins. (Courtesy Dr. T. H. Benzinger.)

hypothalamic centers to the shivering threshold even when the hypothalamic temperature itself is still on the hot side of normal. Here again, one can understand the value of the control system because a cold skin temperature would soon lead to a deeply depressed body temperature unless heat production were increased. Thus, a cold skin temperature actually "anticipates" a fall in internal body temperature and prevents this.

Behavioral Control of Body Temperature

Aside from the subconscious mechanisms for body temperature control, the body has another temperature-control mechanism that is even more potent. This is *behavioral control of temperature*, which can be explained as follows: Whenever the internal body temperature becomes too high, signals from the temperature-controlling areas in the brain give the person a psychic sensation of being overheated. Conversely, whenever the body becomes too cold, signals from the skin and probably also from some deep body receptors elicit the feeling of cold discomfort. Therefore, the person makes appropriate environmental adjustments to re-establish comfort, such as moving into a heated room or wearing well-insulated clothing in freezing weather. This is a much more powerful system of body temperature control than most physiologists have acknowledged in the past. Indeed, this is the only really effective mechanism to maintain body heat control in severely cold environments.

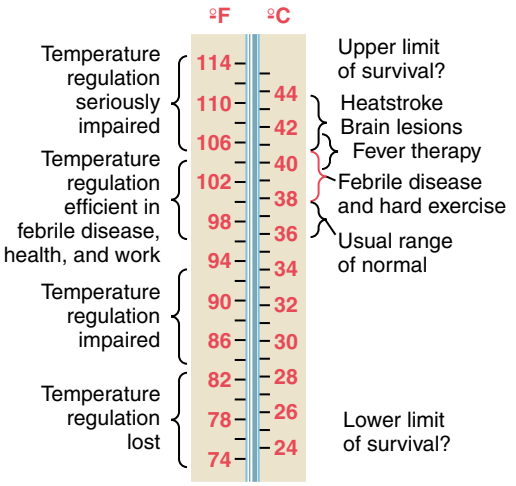


Figure 73-10 Body temperatures under different conditions. (Redrawn from DuBois EF: Fever. Springfield, Ill: Charles C Thomas, 1948.)

Local Skin Temperature Reflexes

When a person places a foot under a hot lamp and leaves it there for a short time, *local vasodilation* and mild *local sweating* occur. Conversely, placing the foot in cold water causes local vasoconstriction and local cessation of sweating. These reactions are caused by local effects of temperature directly on the blood vessels and also by local cord reflexes conducted from skin receptors to the spinal cord and back to the same skin area and the sweat glands. The *intensity* of these local effects is, in addition, controlled by the central brain temperature controller, so their overall effect is proportional to the hypothalamic heat control signal *times* the local signal. Such reflexes can help prevent excessive heat exchange from locally cooled or heated portions of the body.

Regulation of Internal Body Temperature Is Impaired by Cutting the Spinal Cord. After cutting the spinal cord in the neck above the sympathetic outflow from the cord, regulation of body temperature becomes extremely poor because the hypothalamus can no longer control either skin blood flow or the degree of sweating anywhere in the body. This is true even though the local temperature reflexes originating in the skin, spinal cord, and intra-abdominal receptors still exist. These reflexes are extremely weak in comparison with hypothalamic control of body temperature.

In people with this condition, body temperature must be regulated principally by the patient's psychic response to cold and hot sensations in the head region—that is, by behavioral control of clothing and by moving into an appropriate warm or cold environment.

Abnormalities of Body Temperature Regulation

Fever

Fever, which means a body temperature above the usual range of normal, can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature-regulating centers. Some causes of fever (and also of subnormal body temperatures) are presented in Figure 73-10. They include bacterial diseases, brain tumors, and environmental conditions that may terminate in heatstroke.

Resetting the Hypothalamic Temperature-Regulating Center in Febrile Diseases—Effect of Pyrogens

Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide toxins released from bacterial cell membranes, can cause the set-point of the hypothalamic thermostat to rise. Substances that cause this effect are called *pyrogens*. Pyrogens released from toxic bacteria or those released from degenerating body tissues cause fever during disease conditions. When the set-point of the hypothalamic temperature-regulating center becomes higher than normal, all the mechanisms for raising the body temperature are brought into play, including heat conservation and increased heat production. Within a few hours after the set-point has been increased, the body temperature also approaches this level, as shown in Figure 73-11.

Mechanism of Action of Pyrogens in Causing Fever—Role of Cytokines. Experiments in animals have shown that some pyrogens, when injected into the hypothalamus, can act directly and immediately on the hypothalamic temperature-regulating center to increase its set-point. Other pyrogens function indirectly and may require several hours of latency before causing their effects. This is true of many of the bacterial pyrogens, especially the *endotoxins* from gram-negative bacteria.

When bacteria or breakdown products of bacteria are present in the tissues or in the blood, they are *phagocytized by the blood leukocytes, by tissue macrophages*, and *by large granular killer lymphocytes*. All these cells digest the bacterial products and then release cytokines, a diverse group of peptide signaling molecules involved in the innate and adaptive immune responses. One of the most important of these cytokines in causing fever is *interleukin-1 (IL-1)*, also called *leukocyte pyrogen* or

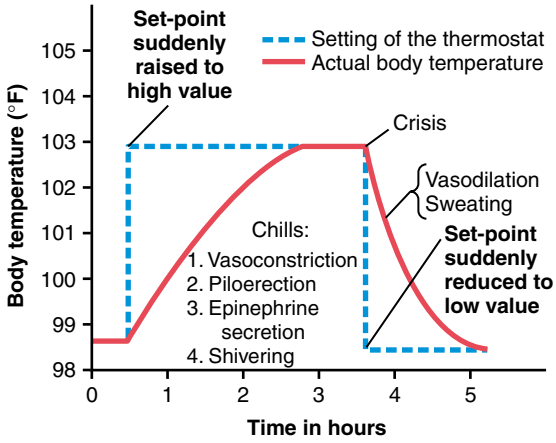


Figure 73-11 Effects of changing the set-point of the hypothalamic temperature controller.

endogenous pyrogen. Interleukin-1 is released from macrophages into the body fluids and, on reaching the hypothalamus, almost immediately activates the processes to produce fever, sometimes increasing the body temperature a noticeable amount in only 8 to 10 minutes. *As little as one ten millionth of a gram of endotoxin lipopolysaccharide* from bacteria, acting in concert with the blood leukocytes, tissue macrophages, and killer lymphocytes, can cause fever. The amount of interleukin-1 that is formed in response to lipopolysaccharide to cause fever is only a few nanograms.

Several experiments have suggested that interleukin-1 causes fever by first inducing the formation of one of the prostaglandins, mainly prostaglandin E_2, or a similar substance, which acts in the hypothalamus to elicit the fever reaction. When prostaglandin formation is blocked by drugs, the fever is either completely abrogated or at least reduced. In fact, this may be the explanation for the manner in which aspirin reduces fever because aspirin impedes the formation of prostaglandins from arachidonic acid. Drugs such as aspirin that reduce fever are called *antipyretics*.

Fever Caused by Brain Lesions. When a brain surgeon operates in the region of the hypothalamus, severe fever almost always occurs; rarely, the opposite effect, hypothermia, occurs, demonstrating both the potency of the hypothalamic mechanisms for body temperature control and the ease with which abnormalities of the hypothalamus can alter the set-point of temperature control. Another condition that frequently causes prolonged high temperature is compression of the hypothalamus by a brain tumor.

Characteristics of Febrile Conditions

Chills. When the set-point of the hypothalamic temperature-control center is suddenly changed from the normal level to higher than normal (as a result of tissue destruction, pyrogenic substances, or dehydration), the body temperature usually takes several hours to reach the new temperature set-point.

Figure 73-11 demonstrates the effect of suddenly increasing the temperature set-point to a level of 103°F. Because the blood temperature is now less than the set-point of the hypothalamic temperature controller, the usual responses that cause elevation of body temperature occur. During this period, the person experiences chills and feels extremely cold, even though his or her body temperature may already be above normal. Also, the skin becomes cold because of vasoconstriction and the person shivers. Chills can continue until the body temperature reaches the hypothalamic set-point of 103°F. Then the person no longer experiences chills but instead feels neither cold nor hot. As long as the factor that is causing the higher set-point of the hypothalamic temperature controller is present, the body temperature is regulated more or less in the normal manner, but at the high temperature set-point level.

Crisis, or "Flush". If the factor that is causing the high temperature is removed, the set-point of the hypothalamic temperature controller will be reduced to a lower value—perhaps even back to the normal level, as shown in Figure 73-11. In this instance, the body temperature is still 103°F, but the hypothalamus is attempting to regulate the temperature to 98.6°F. This situation is analogous to excessive heating of the anterior hypothalamic-preoptic area, which causes intense sweating and the sudden development of hot skin because of vasodilation everywhere. This sudden change of events in a febrile state is known as the "crisis" or, more appropriately, the "flush." In the days before the advent of antibiotics, the crisis was always anxiously awaited because once this occurred, the doctor assumed that the patient's temperature would soon begin falling.

Heatstroke

The upper limit of air temperature that one can stand depends to a great extent on whether the air is dry or wet. If the air is dry and sufficient convection air currents are flowing to promote rapid evaporation from the body, a person can withstand several hours of air temperature at 130°F. Conversely, if the air is 100 percent humidified or if the body is in water, the body temperature begins to rise whenever the environmental temperature rises above about 94°F. If the person is performing heavy work, the critical *environmental temperature* above which heatstroke is likely to occur may be as low as 85° to 90°F.

When the body temperature rises beyond a critical temperature, into the range of 105° to 108°F, the person is likely to develop *heatstroke*. The symptoms include dizziness, abdominal distress sometimes accompanied by vomiting, sometimes delirium, and eventually loss of consciousness if the body temperature is not soon decreased. These symptoms are often exacerbated by a degree of *circulatory shock* brought on by excessive loss of fluid and electrolytes in the sweat.

The hyperpyrexia itself is also exceedingly damaging to the body tissues, especially the brain, and is responsible for many of the effects. In fact, even a few minutes of very high body temperature can sometimes be fatal. For this reason, many authorities recommend immediate treatment of heatstroke by placing the person in a cold water bath. Because this often induces uncontrollable shivering, with a considerable increase in the rate of heat production, others have suggested that sponge or spray cooling of the skin is likely to be more effective for rapidly decreasing the body core temperature.

Harmful Effects of High Temperature. The pathological findings in a person who dies of hyperpyrexia are local

hemorrhages and parenchymatous degeneration of cells throughout the entire body, but especially in the brain. Once neuronal cells are destroyed, they can never be replaced. Also, damage to the liver, kidneys, and other organs can often be severe enough that failure of one or more of these organs eventually causes death, but sometimes not until several days after the heatstroke.

Acclimatization to Heat. It can be extremely important to acclimatize people to extreme heat. Examples of people requiring acclimatization are soldiers on duty in the tropics and miners working in the 2-mile-deep gold mines of South Africa, where the temperature approaches body temperature and the humidity approaches 100 percent. A person exposed to heat for several hours each day while performing a reasonably heavy workload will develop increased tolerance to hot and humid conditions in 1 to 3 weeks.

Among the most important physiological changes that occur during this acclimatization process are an approximately twofold increase in the maximum rate of sweating, an increase in plasma volume, and diminished loss of salt in the sweat and urine to almost none; the last two effects result from increased secretion of aldosterone by the adrenal glands.

Exposure of the Body to Extreme Cold

Unless treated immediately, a person exposed to ice water for 20 to 30 minutes ordinarily dies because of heart standstill or heart fibrillation. By that time, the internal body temperature will have fallen to about 77°F. If warmed rapidly by the application of external heat, the person's life can often be saved.

Loss of Temperature Regulation at Low Temperatures. As noted in Figure 73-10, once the body temperature has fallen below about 85°F, the ability of the hypothalamus to regulate temperature is lost; it is greatly impaired even when the body temperature falls below about 94°F. Part of the reason for this diminished temperature regulation is that the rate of chemical heat production in each cell is depressed almost twofold for each 10°F decrease in body temperature. Also, sleepiness develops (later followed by coma), which depresses the activity of the central nervous system heat control mechanisms and prevents shivering.

Frostbite. When the body is exposed to extremely low temperatures, surface areas can freeze; the freezing is called *frostbite*. This occurs especially in the lobes of the ears and in the digits of the hands and feet. If the freeze has been sufficient to cause extensive formation of ice crystals in the cells, permanent damage usually results, such as permanent circulatory impairment and local tissue damage. Often gangrene follows thawing, and the frostbitten areas must be removed surgically.

Cold-Induced Vasodilation Is a Final Protection Against Frostbite at Almost Freezing Temperatures. When the temperature of tissues falls almost to freezing, the smooth muscle in the vascular wall becomes paralyzed because of the cold itself, and sudden vasodilation occurs, often manifested by a flush of the skin. This mechanism helps prevent frostbite by delivering warm blood to the skin. This mechanism is far less developed in humans than in most lower animals that live in the cold all the time.

Artificial Hypothermia. It is easy to decrease the temperature of a person by first administering a strong sedative to depress the reactivity of the hypothalamic temperature controller and then cooling the person with ice or cooling blankets until the temperature falls. The temperature can then be maintained below 90°F for several days to a week or more by continual sprinkling of cool water or alcohol on the body. Such artificial cooling has been used during heart surgery so that the heart can be stopped artificially for many minutes at a time. Cooling to this extent does not cause tissue damage, but it does slow the heart and greatly depresses cell metabolism so that the body's cells can survive 30 minutes to more than 1 hour without blood flow during the surgical procedure.

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