metab

ACCIDENTAL HYPOTHERMIA

Gary Reed, M.D.

Medical Grand Rounds
February 10, 1983
Division of General Internal Medicine
Department of Internal Medicine
University of Texas Health Science Center
Dallas, Texas

Historical Perspectives on Temperature and Its Regulation

The relationship of life and heat has been appreciated for centuries. Ancient Greek philosophers first proposed the theories of "innate" heat with the left ventricle seen as a source of a "central fire" being cooled by inhaled air in the lungs. While the source of the heat was taken for granted, theories proposed in the first and second centuries A.D. were concerned primarily with the source of cooling of the "central fire". The close anatomical relationship to the heart and the warmth of expired air made the lungs the most obvious candidate for this function. These feelings were exemplified by the writings of Galen, who in the second century A.D., proposed that the lungs cooled the body during inspiration, discharged waste products during expiration, and nourished the "animal spirit" during both. The persuasiveness of these philosophers and the lack of refuting data left these theories largely unchallenged until the 17th century A.D.

During the 1600's the influence of chemistry led many physicians to believe that fermentation of the blood in the heart was somehow involved in the generation of heat in the body. John Mayow proposed that air served not to cool the body but provided some essential substance necessary to generate heat. Also during this time, Borelli challenged the concept of the "central fire" when, with the use of the newly developed air thermometers, found essentially no difference between the temperature of the heart and other internal organs.

During the early 18th century, two theories of heat production emerged. Viewing the body as essentially a machine, some suggested that heat was generated by agitation of the blood during its passage through the lungs or by friction of red blood cells against the vessel walls or other blood products. However, no evidence could be generated to support this concept and it was dropped. The chemical theory of heat generation was developed when Lavoisier and de Laplace noted that equal amounts of carbon dioxide were produced by an animal breathing and a burning coal when equal amounts of heat were generated. This suggested that respiration was analogous to combustion, but still it was assumed that the heat was generated in the lungs then transported to the body tissues by the blood.

That warm blooded animals and man could tolerate temperatures higher than their own led investigators to suspect that temperature may be regulated. Currie was perhaps the first to suggest this as seen in the following passage:

> *"There is reason to believe, that while the actual temperature of the human body remains unchanged, its health is not permanent interrupted by the variation of the temperature of the medium that surrounds it; but that a few degrees of increase or diminution of the heat of the system, produces diseases and death. A knowledge therefore of the laws which regulate the vital heat, seems to be the most important branch of physiology". (Currie, 1805)*

By 1800, most authorities accepted the concept of temperature regulation although little was known as to how it was maintained. Most felt that the oxidation of carbon was the source of most animal heat. That the nervous system was involved in temperature production was suggested by Brodie (Brodie, 1812) when he reported that the temperature of pithed animals with respirations maintained fell faster than that of dead animals. Liebig argued that the oxidation of carbon and hydrogen in ingested food or tissues could account for the total of heat produced with the brain necessary only for respiratory movement and not heat production as can be seen from the following excerpt:

> *"The want of just conception of force and effect, and the connection of natural phenomena, has led chemists to attribute a part of the heat generated in the animal body to the action of the nervous system. If this view exclude chemical action, or changes in the arrangements of the elementary particles, as a condition of nervous agency, it means nothing else than to derive the presence of motion, the manifestation of a force, from nothing. But no force, no power can come of nothing". (Liebig, 1852)*

During this time evidence was also accumulating suggesting that peripheral tissues, not the lung, were responsible for most of the heat produced in the body.

The role of the central nervous system in temperature regulation prompted considerable debate. Although evaporation had been proposed as a mechanism to maintain a constant temperature, Edwards felt that a modification in the heat producing process was necessary to explain the ability of man and other animals to tolerate wide variations in environmental temperature (Edwards, 1832). That the brain may modulate heat production and dissipation was perhaps first suggested by Claude Bernard when he proposed the concept of a stable internal environment with the nervous system as its regulator. Noting vasodilation and increased warmth in the ears of rabbits after a section of the cervical sympathetic nerve, he proposed that the nervous system controls not only vasomotor responses, but also heat production (Bernard, 1876). However, others disagreed saying the changes in ear temperature could be explained purely on the basis of changes in blood flow.

By the 1870's it was generally accepted that heat loss was regulated by vasomotor nerves and a medullary center controlling respiratory rate, although debate still existed as to the presence of other heat regulating centers. Lesions at various brain stem levels produced erratic results suggesting to some a more complex reflex activity mediated through the central nervous system (Pembrey, 1898).

Throughout the late 1800's and early 1900's experimental lesions in animals and reports of natural lesions in man suggested thermal regulatory function in the corpus striatum, optic thalamus, pons, corpus

callosum, and the lateral ventricles (Ott, 1884; Barboax, 1921). However, by the 1930's, the hypothalamus was generally accepted as the primary center (Ranson, 1939).

Temperature Regulation

The regulation of body temperature allows homeothermic animals to have considerable independence from environmental temperature and a near constant internal environment despite exposure to a wide range of external conditions. This regulation is necessary for optimal metabolic function because of the temperature dependence of enzymatic reactions present in the body. For example, metabolic activity changes about 25% for every 1^{o} change in temperature. Man's temperature is regulated to an optimal level which is near the maximum temperature tolerated by most metabolically active cells, and consequently a rise of only a few degrees will result in death after a short period of time. A comparable fall in temperature, on the other hand, is usually well tolerated as illustrated in Figure 1.

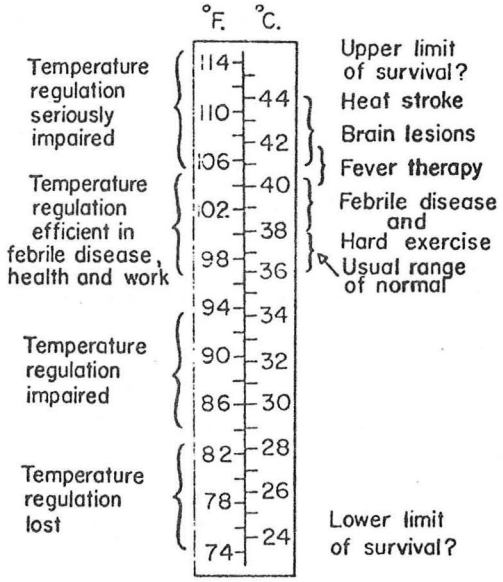


Figure 1. Body temperatures under different conditions illustrating upper and lower limits of survival.

In order to maintain this metabolically optimal temperature without harm to the organism, some mechanism of temperature regulation is obviously necessary.

The transfer of heat between man and the environment falls into evaporative and nonevaporative mechanisms as seen in the following figure.

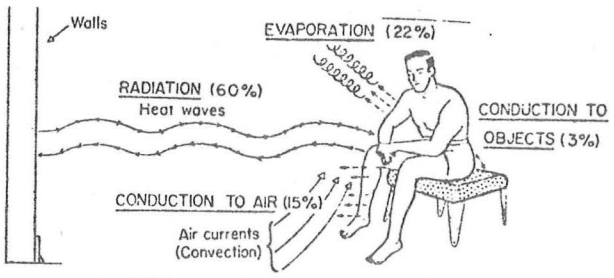


Figure 2. Mechanisms of heat loss from the body

Evaporation accounts for the loss of 0.6 kcal per gram of water evaporated. In a cool environment where heat loss from sweating is minimal, evaporation of insensible perspiration (respiratory tract, oral cavity, and small amounts diffusing through the skin) can account for 20-25% of basal heat production loss. Obviously as heat production increases with cold exposure, this mechanism of heat loss will account for only a small portion of total heat loss to the environment and is not regulated.

Nonevaporative heat transfer is very important in temperature regulation in a cold environment and consists of conduction, convection, and radiation. The amount of heat dissipated by any of these mechanisms is proportional to the temperature difference between man and the environment.

Conduction, the transfer of heat in kinetic form between molecules or atoms of objects in contact, is usually of little consequence unless the subject is immersed in cold water, where the thermal conductivity is 32 times as great as air.

Convection is heat transfer by movement of molecules between two locations of different temperatures. The loss of body heat by this mechanism is greatly increased by wind or water currents and large temperature gradients between the skin and environment.

Radiation is the transfer of heat between objects by nonparticulate means or electromagnetic waves, i.e., the warmth felt from a warm object. The transfer of heat by this means again is greater when a large temperature differential exists between objects. At an ambient temperature of about 20 ^{o}C, heat loss by radiation in man can account for up to 70% of heat produced. The uncovered head is an important source of radiant heat loss amounting to as much as one half of the total body heat production at 4 ^{o}C. The loss of heat by radiation is also proportional to the exposed surface area of the body. For example, more heat is lost to a cold environment in a spread eagle position than a curled position.

That the body can regulate temperature despite the above mechanisms of heat transfer implies some sensor mechanism exists that compares actual body temperature to some reference point and any deviation from this point results in effector mechanisms designed to return the temperature to normal. Normal rectal temperature in man is generally considered to be in the range of 36.5^{o}C to 37.6^{o}C with oral temperatures about 0.6 ^{o}C lower. Temperature, however, may vary even within the rectum because of the close proximity of parts of this organ to the veins draining the lower extremities. This problem must be considered especially in hypothermic patients where the extremities may be significantly cooler than the core. The range of normal temperatures in a healthy population is broad as illustrated in Figure 3 representing the oral temperatures of 276 medical students sitting in class between 8 and 9 a.m. (Ivy, 1944) Also a circadian pattern in body temperature has been reported with the lowest temperatures found in the morning and the warmest in the early afternoon. Although peak daily temperature is the same regardless of season, morning temperatures are lower in the winter than in the summer as shown in figure 4. (Sasaki, 1964)

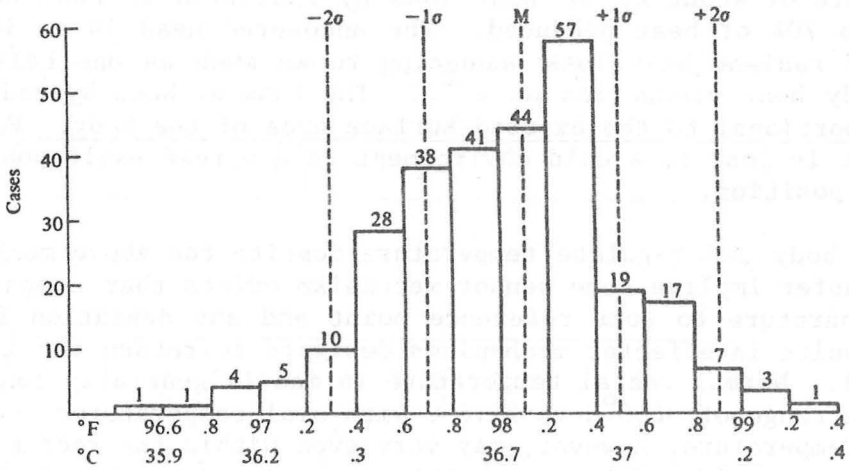


Figure 3. Histogram of oral temperatures of 276 medical students seated in class between 8 and 9 a.m. Mean, 98.1 ± 0.4 °F.

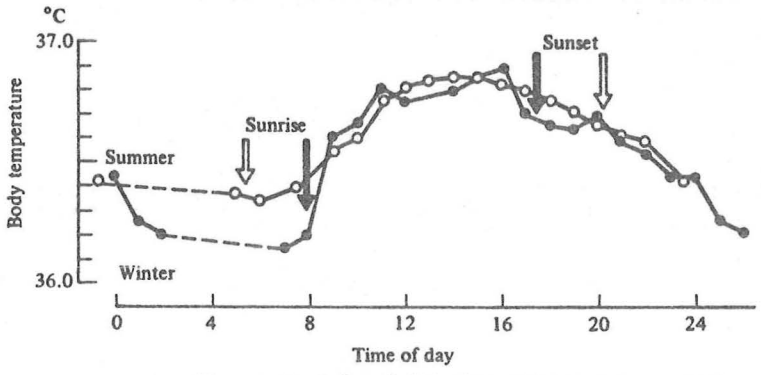


Figure 4. Circadian rhythm in body temperature.

A system for temperature control, as mentioned above, needs a sensor mechanism, controller, and effector mechanisms designed to maintain a constant body temperature. The accepted physiologic counterparts to these components are shown in Table I.

Table I

Sensors	Controller	Effector Mechanisms
Skin Visceral Hypothalamus	Hypothalamus	Behavior Sweating Vasoconstriction Shivering Nonshivering thermogenesis

Thermosensors. Cold and warm thermosensors are located throughout the skin although the density varies considerably with greater numbers present in the skin of the face and hands than the legs and chest. Other cold thermosensors have been identified in the upper gastrointestinal tract, tongue, respiratory system, muscles and spinal cord. Histologically, cold receptors are unmyelinated fibers that divide into a number of unmyelinated, naked nerve endings that penetrate superficially into the cytoplasm of basal epithelial cells (Hensel, 1974).

Physiologically, at least two types of receptors exist, warm and cold, with discharge frequencies increasing as temperature goes up and down respectively as shown in Figure 5 (Iggo, A 1969).

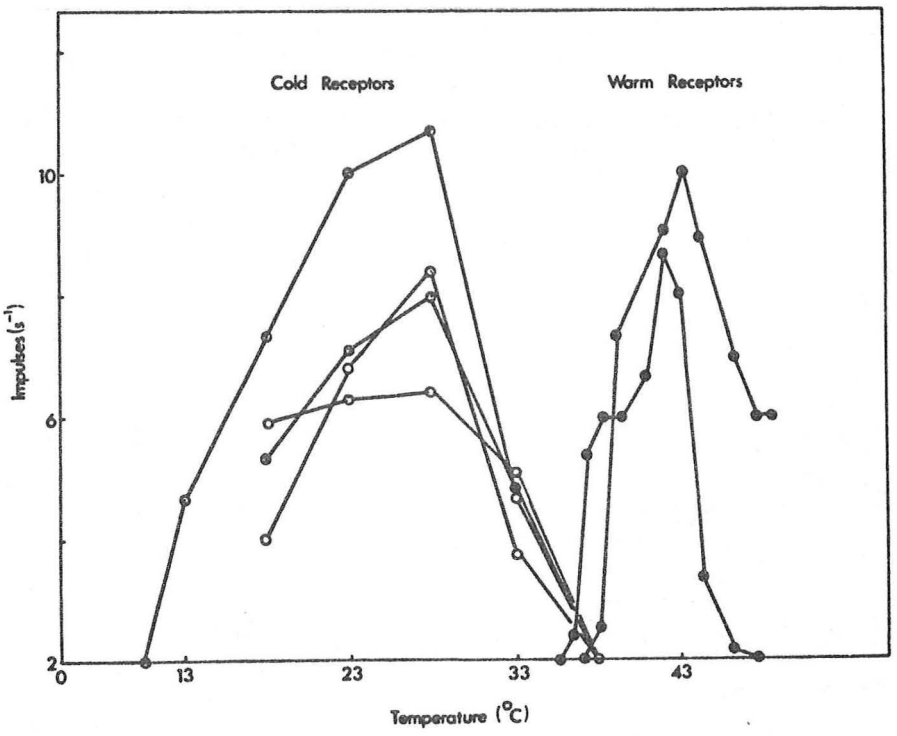


Figure 5. Static sensitivity curves for four cold receptors and two warm receptor preparations in rat skin.

Each cold thermoreceptor has a discharge or firing frequency that is related to both the static temperature and the rate of change of temperature. This discharge frequency seems to be due to the properties of a transmembrane sodium pump (Pierau, 1974). Cold skin thermosensors begin to fire at about 33 °C and as temperature falls, the static temperature discharge frequency increases with maximum discharge rates at about 20 °C. Figure 6 (Hensel, 1952) illustrates this temperature dependence of discharge rate.

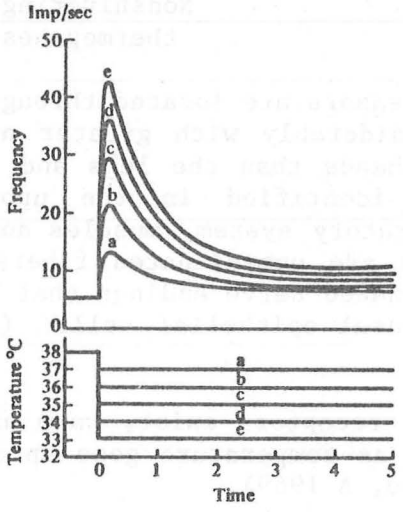


Figure 6. Impulse frequency of single units related to temperature change.

As can be seen, each receptor has a characteristic firing rate for a given temperature with colder temperatures having a faster discharge frequency. The rate of change of temperature also influences discharge rate in that rapid changes in temperature influence the frequency of firing more than slower changes as seen in Figure 7 (Hensel, 1952).

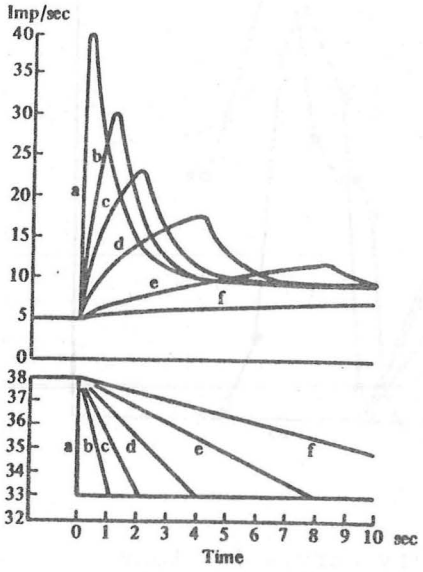


Figure 7. Impulse frequency of single units related to temperature change.

Obviously the net effect is complicated but can be appreciated in Figure 8 (Hensel, 1970) where, for example, a cold thermosensor has a given firing rate at 26 °C. A rapid increase to 30 °C results in silence during the change of temperature with the resumption of a new slower firing rate when the new temperature is reached. On the other hand, a rapid drop in temperature results in a rapid discharge rate followed by a gradual decrease to a new frequency, faster than that of the higher temperature.

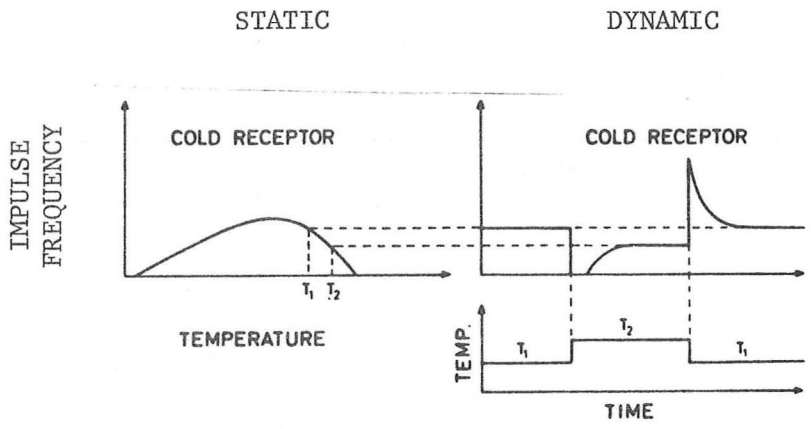


Figure 8. Generalized response of cutaneous cold receptors to constant temperatures (static response) and to rapid temperature changes (dynamic response).

The modification and transmission of the above information to the central nervous system occurs, along with pain sensation, through the dorsal nerve roots to the lateral spinothalamic tracts and eventually the hypothalamus and cortex via the thalamocortical system. Cortical stimulation by this system results in conscious temperature sensation and behavioral changes that reduce heat loss.

Hypothalamus. The role of the hypothalamus in the regulation of body temperature is well established. This area receives information regarding body temperature from the entire body, senses the temperature of arterial blood, and coordinates the effector systems designed to generate and maintain temperature. Multiple neuronal systems provide input from peripheral and cutaneous thermoreceptors, spinal thermoreceptors, midbrain reticular formation, brainstem monoaminergic pathways, and the limbic system. Anatomically, data suggest that at least two areas are involved in this complex process. A group of cells in the posterior hypothalamus, the "heat maintenance" center, receives impulses from peripheral cold thermoreceptors and when stimulated, controls and coordinates the mechanism for heat production and

conservation, i.e., shivering, vasoconstriction, and metabolic rate. When stimulated, this center also sends inhibitory impulses to the anterior hypothalamus. When this "heat maintenance" center is damaged experimentally or naturally, the ability to conserve heat or increase heat production in the cold is lost, while heat losing mechanisms remain relatively normal.

A second region in the preoptic/anterior hypothalamus seems to be more involved in heat loss mechanisms and possibly contains the "thermostat" postulated to be necessary for temperature control. Experimental damage to this "heat loss" center results in an inability to lose heat and maintain a normal temperature in a hot environment while the ability to conserve and generate heat in a cold environment is retained. This area also contains warm and cold thermosensors that monitor the temperature of arterial blood as it passes through this region of the brain. (Wit, 1967; Wit, 1968; Boulant, 1974) If cold receptors are stimulated by a fall in arterial blood temperature, impulses are sent to the posterior hypothalamus that initiate mechanisms of heat production and conservation. Warm thermoreceptor stimulation, on the other hand, stimulates sweating, vasodilatation, and other means of heat loss. This can be appreciated in Figure 9 (Nakayama, 1963) where hypothalamic warming results in an increase in the discharge frequency of a thermosensitive neuron in the preoptic area (curve A) and thereafter an increase in respiratory rate (curve B). The interaction between the effects of the peripheral and central thermosensors is complex. Heat production at any given central temperature can be modified significantly by changing skin temperature as illustrated in Figure 10. (Benzinger, 1963)

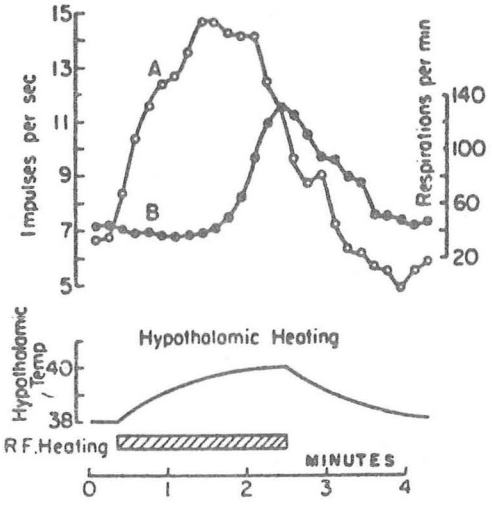


Figure 9. Discharge frequency of a neuron in the preoptic region (Curve A) and change respiratory rate (Curve B) in relation to hypothalmic temperature.

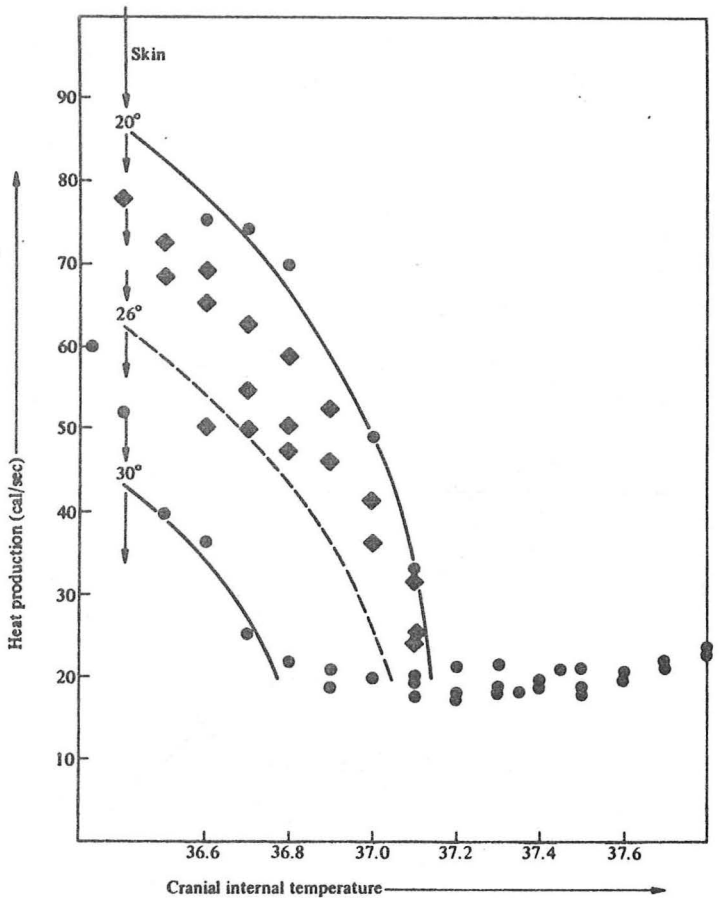
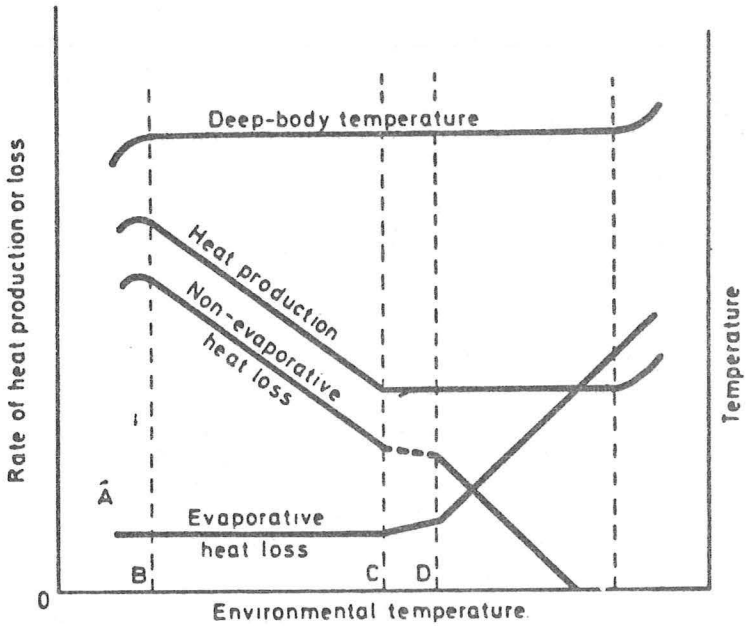


Figure 10. Results from experiments in the human calorimeter showing that the relationship between heat production and cranial internal temperature is modified by the skin temperature.

There is evidence that the "thermostat" in the anterior hypothalamus is set by chemical mediators, although different mediators probably exist in different species. Norepinephrine, 5-hydroxytryptamine, sodium and calcium ions, and prostaglandin E_1 have been suggested. (Myers, 1971; Feldberg and Saxena, 1971)

The concept of a "thermo neutral zone" is important in understanding the development of clinical hypothermia. In clinical terms, this zone represents the range of ambient temperature within which metabolic rate is at a minimum and temperature regulation is achieved by nonevaporative physical processes alone. This zone, represented by CD in Figure 11 (Mount, 1974), is a fairly narrow range in which autonomic (skin blood flow) and behavioral responses are the most important means of temperature regulation. At lower temperatures, evaporative heat loss remains minimal while nonevaporative heat loss is paralleled by an

increase in heat production to maintain a normal core temperature. The zone of hypothermia (A) is reached when environmental temperature falls below a critical temperature (B) where metabolic rate is at a maximum.



Mechanisms of heat production and conservation. The effector mechanisms set in action by the hypothalamus in response to peripheral or central cold receptor stimulation are complex but can easily be divided into means to decrease heat loss and means to increase heat production.

When man is placed in a cold environment, the first mechanisms that comes into play to maintain temperature is a reduction in heat lost to the environment primarily through behavioral and circulatory adjustments. Behavioral adaptations to conscious perceptions of low skin temperature in man are obvious and include posturing, seeking of shelter, clothing, physical activity, and migration. Circulatory responses to decrease heat loss fall primarily into two classes. One is to increase the insulating capability of the skin and subcutaneous tissues by shunting blood away from these tissues by vasoconstriction. This is accomplished primarily through activation of the sympathetic nervous system with some influence by the adrenal medulla via circulating catecholamines and as a direct influence of cold. This peripheral vasoconstriction increases the thickness and decreases the

thermal conductivity of an outer "shell" to protect the temperature of the inner "core" consisting primarily of the skull, thoracic and abdominal viscera. This concept of a core with its protecting shell is illustrated in Figure 12.

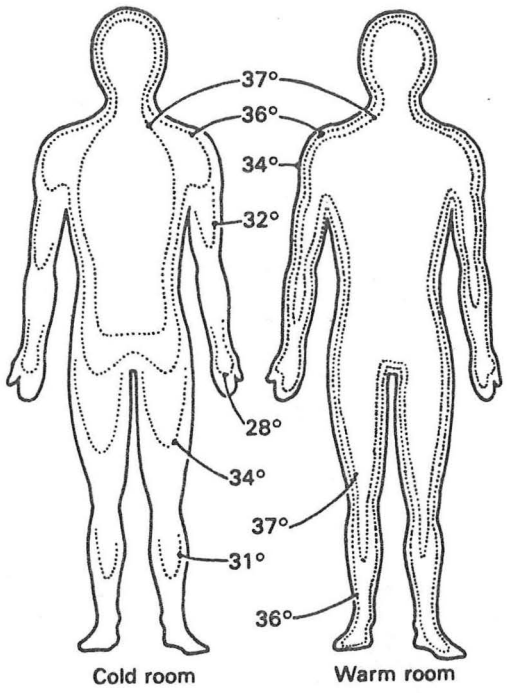


Figure 12. Schematic representation of temperature gradients forming a "core" and "shell" in a man in a cold and warm environment.

This insulating vasoconstriction can be intense and reaches a near maximum with only a small fall in core or environmental temperature. With further drops in temperatures, other mechanisms must be brought into play to maintain temperature (Figure 13).

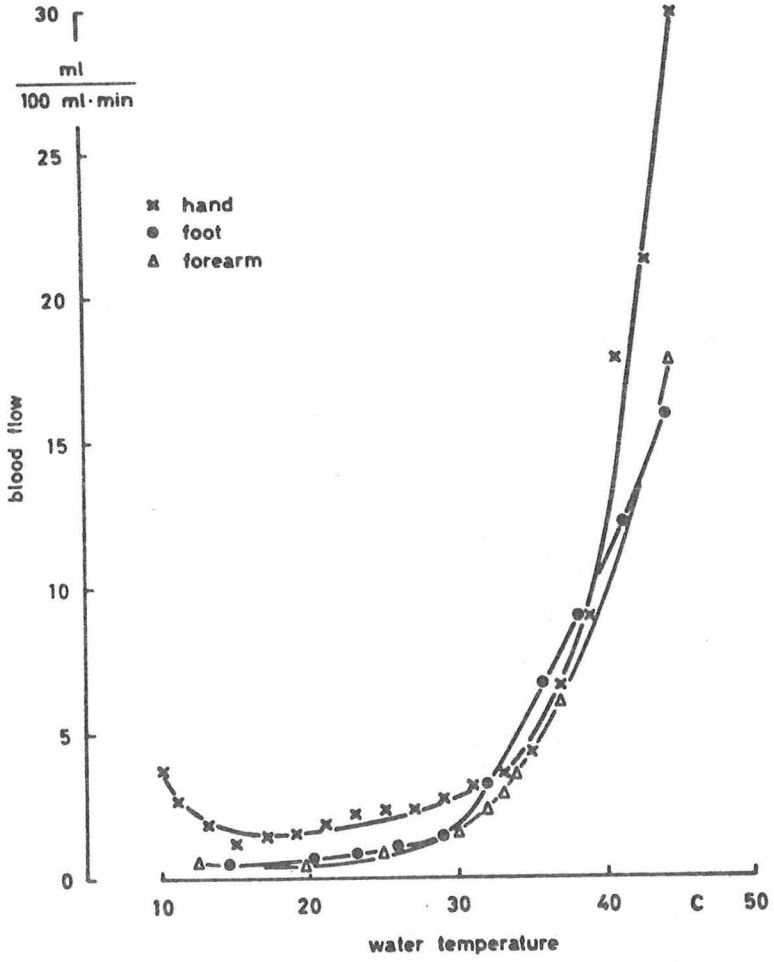


Figure 13. Relationship between blood flow in the human hand, foot, and forearm, and water temperature of the plethysmograph (Thauer, 1963).

A second vascular mechanism which may be important in man is a counter-current heat exchange system in the extremities. Figure 14 illustrates how this can occur. In a warm environment, superficial veins dilate to facilitate heat transfer from the vascular system to the environment. With cold temperatures, however, veins in close proximity to the arteries may become more dilated with arterial heat transferred to them in the proximal extremities and returned to the central (core) circulation. This counter-current mechanism is highly developed in some homeotherms but its relative importance in man is largely unknown.

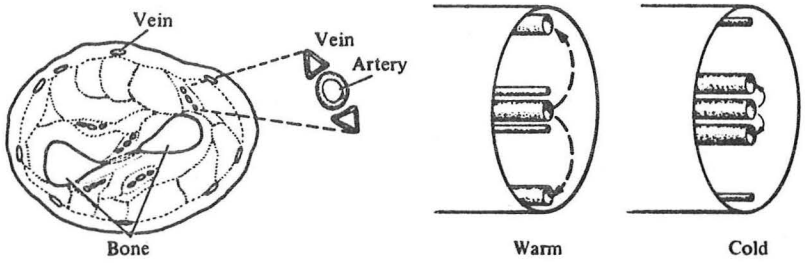


Figure 14. Heat exchange system in the forearm with a diagrammatic representation of the shift in venous blood flow from superficial vessels in warm surroundings to deep-lying vessels in the cold.

As environmental temperature falls below the thermoneutral zone and peripheral vasoconstriction is near maximum, the body begins to increase heat production by metabolic processes as seen in Figure 15.

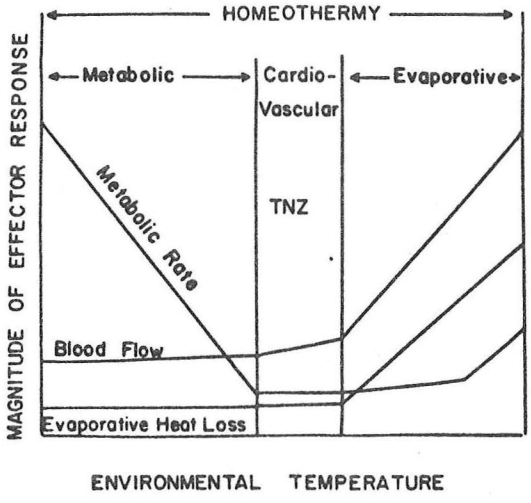


Figure 15. General thermoregulatory profile for a hypotheleal homeotherm indicating primary effector responses.

The acute response to a drop in environmental temperature is shivering. This synchronous contraction and relaxation of antagonistic muscle groups can increase the heat production by the body several fold. Shivering does not transform all of the heat produced into an increase in body temperature because of the loss of insulation and increased heat loss from convection. Shivering is the primary means of increasing heat production when homeotherms are acutely exposed to cold or cold acclimatized homeotherms are exposed to temperatures below the temperature of acclimitization. Shivering thermogenesis is mediated primarily through the neural pathways that enervate skeletal muscle with probable contribution from circulating catecholamines.

With prolonged exposure to cold, the relative importance of shivering thermogenesis gives way to a rise in heat production by nonshivering thermogenesis (Figure 16). The mechanisms by which heat production is increased are poorly understood but involve a synergistic action of thyroxine and catecholamines on the metabolism of many tissues (Figure 17) and substrates.

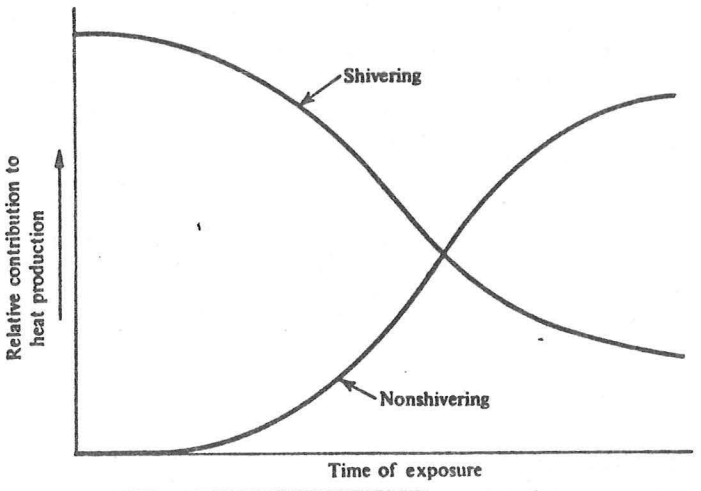


Figure 16. Schematic diagram of the change-over from shivering to nonshivering heat production with time of exposure.

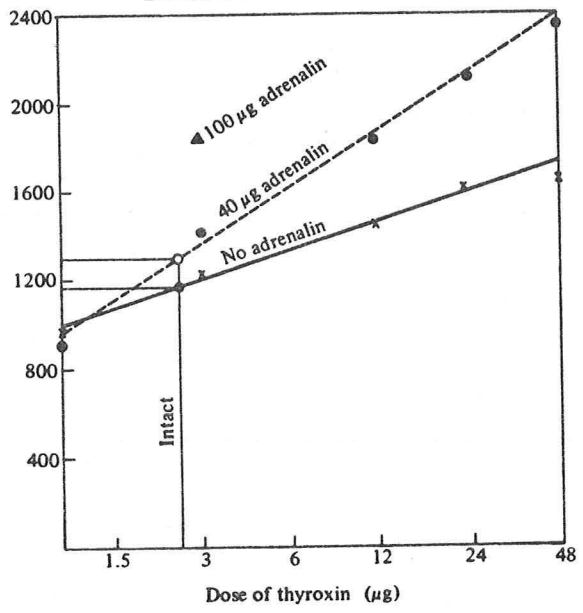


Figure 17. Regression of oxygen consumption of thyroidectomized rats treated with various doses of epinephrine plotted against the dose of thyroxin on a logarithmic scale. (Swanson, 1957)

Obviously the above mechanisms of temperature regulation require the coordination of several organ systems, primarily cardiovascular and neuroendocrine. Acutely, temperature regulation is mediated by neural mechanisms concerned with vasoconstriction, sweating, shivering and substrate provision. Neuroendocrine mechanisms that increase nonshivering thermogenesis become important after more prolonged exposure. Cold acclimatization involves circulatory adjustments to protect certain parts of the body, metabolic adaptations to increase heat production and behavioral changes to minimize cold stress and discomfort.

Pathophysiology of Hypothermia

When heat loss is in excess of maximum heat production or when heat generation/regulation is inadequate in a cool environment, hypothermia obviously develops. While clinically important hypothermia is probably not specifically lethal to individual cells, derangements of metabolic activity and organ function will result in the death of the organism when critical temperatures are reached. A thorough understanding of the pathophysiology of these changes is vital for any clinician treating or resuscitating hypothermic patients. A sophisticated study of these patients is obviously difficult given their critical condition. Consequently, much of the data presented below is the result of elaborate studies on patients undergoing induced hypothermia for therapeutic reasons. Obviously, controlled hypothermia in a clinical setting is markedly different from that resulting from exposure and metabolic derangements. However, many generalizations can be made if such differences are appreciated.

Oxygen consumption and metabolic rate. Oxygen consumption and metabolic rate fall as temperatures decline, primarily because of the temperature dependence of metabolic processes. The decline in oxygen consumption with hypothermia is thought to be exponential (Horvath, 1953; Fairley, 1961; Abbott, 1977) as illustrated in Figure 18 (Rosomoff, 1964), although a linear relationship has been suggested by some (Adolph, 1950; Bigelow, 1950; Prakash, 1978).

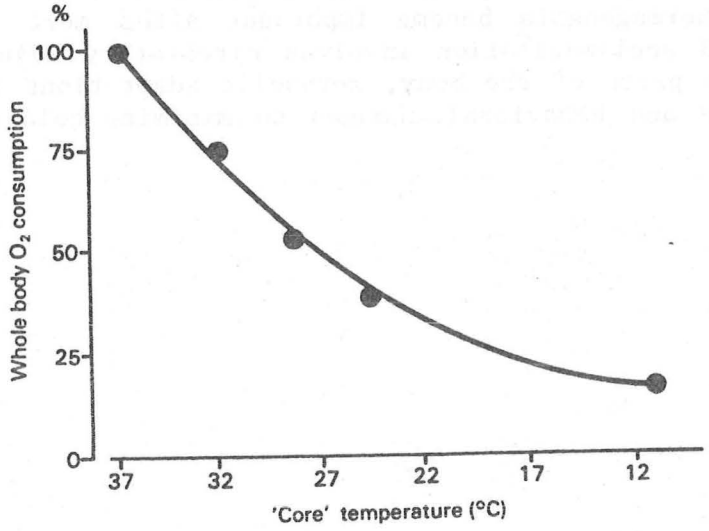


Figure 18. Curve showing the reduction in whole body O_2 consumption during hypothermia in man.

Table II illustrates the proportional fall in oxygen consumption by various organs as temperature declines (Blair, 1965).

Table II: Change in oxygen consumption during hypothermia (percent of normal).

	TEMPERATURE °C				
	32°	30-28°	25°	20°	10°
Total	70	50-40	30	20	10
Heart	80	70-65	50	40	13
Brain	75	60-50	30	20	15-10
Kidney	50	40	30	25	10-5
Liver	80	60-50	40	20	15

This fall in metabolism and the fact that metabolic processes are depressed more than the diffusion of metabolites account for the successful resuscitation of many hypothermic patients after prolonged cardiorespiratory collapse.

The values of total oxygen consumption illustrated above have generally been made under artificial conditions where shivering and voluntary muscle movement have been prevented. In the setting of accidental hypothermia, this generally occurs only after a significant lowering of body temperature has occurred. Early in the development of hypothermia, an increase of up to 15-fold in the total metabolic rate can occur due to shivering, voluntary muscle activity, and involuntary muscular rigidity (Hervey, 1973).

The effects of hypothermia on oxygen availability are complex. As temperature falls, oxygen solubility in plasma (Hervey, 1973; Abbott, 1977) and tissue binding increase favoring oxygen availability to tissues. As blood is cooled, however, the oxyhemoglobin curve is shifted to the left creating an unfavorable relationship between oxygen supply and demand. In general, these influences offset each other and oxygen supply is adequate for the reduced metabolic demand. These effects can be detrimental, however, during rewarming when relatively warm tissues which are metabolically active are perfused by cold blood (Fisher, 1977).

Cardiovascular System - When a person is exposed to a cold environment and body temperature falls slightly, the cardiovascular system responds with tachycardia and a moderate increase in central venous pressure, blood pressure, peripheral vascular resistance and cardiac output. These changes are due primarily to the increase in metabolic demand by shivering muscle and an increase in sympathoadrenal outflow elicited by fear, fighting responses and the drop in skin temperature. As hypothermia progresses, however, the primary changes in the

cardiovascular system are depressive. These changes again are largely protective allowing the myocardium to better tolerate prolonged periods of anoxia and substrate deprivation.

Cardiac output falls progressively as hypothermia develops being about 70% of normal at 31 °C. This reduction in cardiac output is due primarily to a fall in ventricular rate with stroke volume being normal (Goodyer, 1965; Rittenhouse, 1971) or perhaps slightly reduced (Prec, 1949). With rewarming, cardiac output tends to rise progressively (Rittenhouse, 1971) although a return to normal may be delayed.

Heart rate falls progressively as temperature declines (Gunton, 1956) and eventually results in cardiac standstill. This is due to a depression of atrial and ventricular pacemaker activity with a relative prolongation of systole over diastole (Berne, 1953; Hervey, 1973). The slow systolic time in many patients results in a flat pulse wave making the pulse difficult to palpate even when direct measurements of blood pressure are normal.

Despite the decline in cardiac output and heart rate, blood pressure usually remains remarkably normal (Blair, 1969) because of a marked rise in peripheral vascular resistance (Kuhn, 1959; Goodyer, 1965; Benzing, 1968). This increase in vascular tone is due to sympathetic stimulation, an increase in circulating catecholamines, a direct effect of the cold on peripheral vessels and an increase in blood viscosity with hemoconcentration. This vasoconstriction is generalized but not uniform in that blood is shunted from most tissues to support the heart and central circulation (Rudy, 1972). Circulatory reflexes supporting blood pressure are maintained to about 28 °C although the response to hypotension is blunted below about 30 °C. In fact, the most common situation to encounter hypotension is during treatment in the form of "rewarming shock" when the intense vasoconstriction is lost and peripheral resistance falls dramatically. Hypothermic vasoconstriction results in increased work by the myocardium, but an increase in myocardial efficiency and the decrease in metabolic demands make the lower cardiac output and rate more than adequate in most instances.

In summary, the cardiovascular response to cold stress has two phases. Acutely, exposure results in sympathetic stimulation with an increase in heart rate, cardiac output, peripheral resistance, blood pressure and central venous pressure. As core temperature falls, cardiovascular depression is then seen with a fall in heart rate and cardiac output and a return to normal of blood pressure and central venous pressure (Blair, 1969).

Hypothermia causes a decrease in oxygen and metabolic demand of the myocardium as with other tissues. The effect on myocardial blood flow is, however, variable. Surface cooling to 25 - 28 °C has been reported to decrease coronary blood flow with further cooling causing a rise (Berne, 1954; Berne, 1959). Central cooling to the same degree, on the other hand, increases coronary blood flow down to 10 °C because of a

decrease in vascular resistance (Berne, 1959; Bernhard, 1960; Mangiardi, 1966). The clinical significance of changes in blood flow and substrate availability is difficult to establish. In 1978, Carlson reported an increase in creatine phosphokinase MB isoenzyme in patients with severe hypothermia without evidence of myocardial infarction, suggesting myocardial cellular damage. However, the net effect is probably that despite changes in blood flow and substrate availability, the delivery of oxygen and nutrients to the myocardium is generally adequate for the reduced demand.

Cardiac arrhythmias, especially atrial fibrillation, (Gunton, 1956) are very common with temperatures less than 30 ^{o}C, and in general as core temperature falls, the incidence of arrhythmias increases. As temperature falls, the action potential of myocardial cells and conduction fibers lengthens with the appearance of a characteristic dip in the early part of the plateau phase. Maclean and Emslie-Smith have suggested these changes are due to ion flux changes across the sarcolemma (Maclean, 1974) and unrelated to changes in blood pH or electrolytes.

The appearance of atrial arrhythmias does not necessarily indicate the presence of organic heart disease but only the metabolic and physiologic changes seen with hypothermia. These arrhythmias usually are benign and resolve without specific treatment as core temperature rises (Gunton, 1956). Correction of metabolic derangements, digoxin, or quinidine may potentiate the conversion to sinus rhythm although drug treatment is usually unnecessary. Ventricular ectopic beats are less commonly seen and are usually isolated premature beats. Again, the appearance of ventricular ectopy does not indicate intrinsic heart disease but may herald ventricular fibrillation (Schwab, 1964). Ventricular fibrillation is considered the cause of death of many patients with hypothermia, but its actual contribution is obviously difficult to judge because most deaths are unmonitored. The incidence increases as temperature decreases being very rare at temperatures greater than 32 ^{o}C and an imminent danger if less than 28 ^{o}C (Vandam, 1959; Mouritzen, 1965). The exact cause of this arrhythmia is unknown but some postulate that differences in temperature between the endocardium and epicardium (Lloyd, 1974) may vary conduction rates enough to initiate a reentry circuit. The incidence of ventricular fibrillation is related also to the presence of hypoxia (Swan, 1955), acidosis, hypercapnia, and electrolyte disorders. External or internal body stimulation, such as urethral catheterization, movement, endotracheal intubation and vascular catheterization also predispose to the development of this arrhythmia. Like other tissues, the hypothermic environment allows the myocardium to tolerate cardiovascular collapse and anoxia longer than at room temperature, making vigorous resuscitative efforts important despite seemingly prolonged ventricular fibrillation or asystole (Southwick, 1980; DaVee, 1980).

Electrocardiographic changes are very common in hypothermia and many times may even suggest the diagnosis. Mechanical artifacts due to

extracardiac muscle activity frequently obscure low voltage complexes and make the detection of EKG changes difficult unless an esophageal lead is used. Although sinus tachycardia may be seen with mild degrees of hypothermia, its presence should suggest complicating factors such as gastrointestinal bleeding, drug overdose, carbon monoxide poisoning or sepsis. As a general rule, the EKG changes associated with significant hypothermia reflect the depressing effect upon rhythmicity and conductivity. An almost linear fall in atrial and ventricular rate develops with progressive hypothermia. This effect on cardiac rhythm is probably a direct effect of cold temperatures since it is not influenced by vagotomy or atropine (Jacob, 1978). As core temperature falls, higher rhythmic centers are depressed earlier than lower centers. Myocardial conductivity is seriously depressed with any significant hypothermia and is manifest by prolonged PR, QRS, and QT intervals (Gunton, 1956). QT interval prolongation is very common and may remain prolonged for several days (Talbott, 1941) after euthermia has been restored. This increase is unrelated to changes in serum pH or calcium. Nonspecific changes in the ST segment and T waves are also common (Falk, 1977) and may persist days after rewarming. The most consistent changes in the electrocardiogram are widening of the base of the QRS interval and J point deflection leading to so-called Osborn waves (Osborn, 1953)as illustrated in Figure 19.

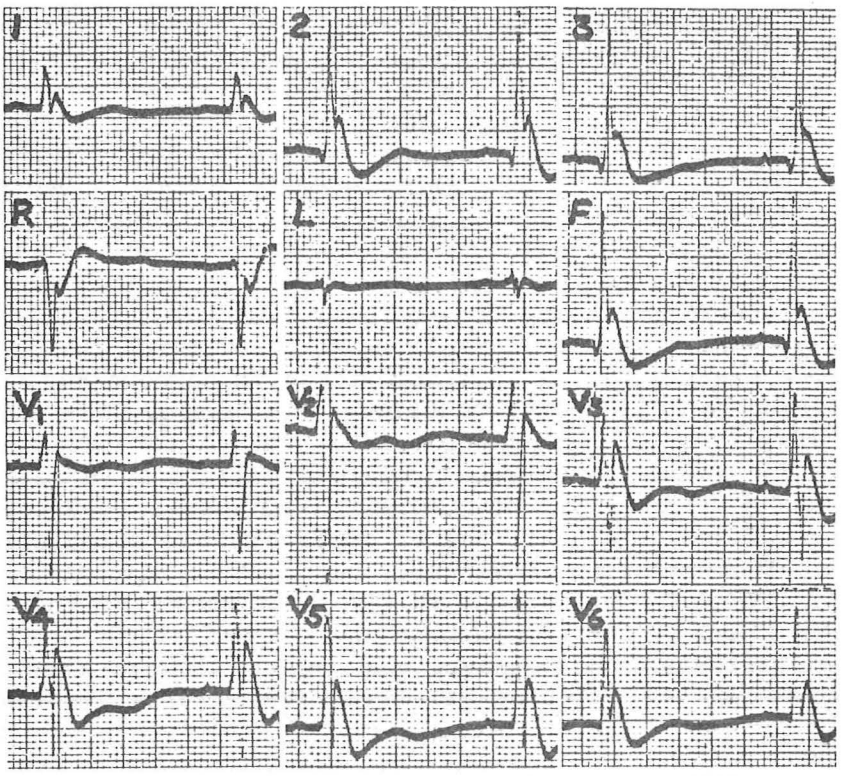


Figure 19. Osborn waves or "J deflection" in hypothermia

These are generally best seen in leads reflecting the left ventricle and are probably due to alterations in ion flux in the myocardial sarcolemma. Contrary to previous belief, these deflections do not herald the onset of ventricular fibrillation and can be seen with hypothermia unrelated to exposure. (Thompson, 1977; Trevino, 1977; Drake, 1980).

Central Nervous System. In general, the metabolic rate of the brain declines as hypothermia develops, although the fall may be blunted if shivering is present. This fall in metabolic demand allows for successful cerebral resuscitation even after prolonged periods of anoxia and circulatory arrest at very low temperatures (Cohen, 1977; Haka-Ikse, 1978; Clarkson, 1980; Derbyshire, 1980; Young, 1980). Suzuki, et al. (1979), have reported several neurosurgical patients who tolerated clamping of the middle cerebral artery for up to 40 minutes at 30 ^{o}C without neurological sequelae. With hypothermia, cerebral blood flow declines due to a combination of factors including a fall in cardiac output and an increase in cerebrovascular resistance (Ehrmantraut, 1957) and blood viscosity. Cerebrospinal fluid volume, total brain volume and cerebral venous pressure all decrease due to the shifts in fluid compartments. Cerebrospinal fluid pleocytosis is very uncommon (Fischbeck, 1981).

As with other organs, hypothermia generally results in a depression of the central nervous system. Central nervous system signs are extremely variable, but as core temperature falls to about 32 ^{o}C, a progressive decline in mental status develops associated with gait ataxia, tremulous speech, normal to hyperactive deep tendon reflexes and appropriate pupillary responses. Below 32 ^{o}C, deep tendon reflexes become less active as the patient develops dysarthria and stupor. Around 30 ^{o}C, movements become delayed and pupillary responses become sluggish. At this point, the patient usually will be able to answer simple questions although response time will be delayed and perseveration may be present. Below 28 ^{o}C, the patient may appear awake and respond to noxious stimulation but usually will demonstrate little spontaneous movement and response to verbal stimulation. Below 26 ^{o}C, many patients are unresponsive to any stimulation and pupils become very sluggish or fixed and deep tendon reflexes diminish. This depression of the deep tendon reflexes is characterized by a prolongation of the contraction and relaxation phases (Maclean, 1973). Babinski responses remain flexor to about 26 ^{o}C with usually no response elicited at lower temperatures. An extensor response is very unusual and should suggest a complicating condition (Fischbeck, 1981). Hoffman's sign is positive to about 30 ^{o}C and thereafter disappears.

With the development of hypothermia, shivering begins and reaches a maximum at 32 - 33 ^{o}C. Below 30 - 32 ^{o}C, however, shivering ceases and muscle rigidity becomes prominent (Duguid, 1961; Andrews, 1964; Exton-Smith, 1973) sometimes causing opisthotonos.

A summary of the central nervous system responses to hypothermia is outlined in Table III. (from Fischbeck, 1981)

Table III: Central Nervous System Manifestations of Hypothermia

32 - 35 °C	Confused, lethargic Normal deep tendon reflexes Corneal and pupillary responses normal
27 - 32 °C	Responds verbally Normal or slightly depressed deep tendon reflexes Pupils normal or sluggish Muscle tone normal or slightly increased
20 - 27 °C	No verbal responses Normal or diminished response to noxious stimuli Pupils sluggish or fixed Depressed deep tendon reflexes Increased muscle tone

Electroencephalographic changes have been described during induced hypothermia although their relevance to accidental exposure is unknown. As the core temperature drops to less than 28 °C, there is a progressive slowing of the electroencephalographic pattern with theta activity and disorganized high voltage delta activity. Electrical activity usually ceases altogether at 15 - 20 °C. A flat EEG is clearly not an indicator of cerebral death as a reversal of the above changes may be seen with rewarming (Cohen, 1977).

Respiratory Function. As with other organ systems, the pulmonary response to the early phases of hypothermia or its causes is one of stimulation with an increase in respiratory rate and subsequent respiratory alklalosis. After this initial response, there is a fall in respiratory rate (Blair, 1964), vital capacity and minute ventilation that is proportional to the fall in metabolic rate associated with hypothermia. During this phase, respirations become shallow and slow. Although difficult to prove, the frequent association of hypothermia and carbon dioxide retention with respiratory acidosis implies some abnormality of respiratory control. Hypothermia has little direct effect on the mechanical properties of the lung other than mild bronchodilatation and a decrease in compliance (Vapaaviori, 1962). Cooling also causes an alpha mediated increase in pulmonary vascular resistance and pressure (Stern, 1970). Airway resistance usually remains normal unless complications develop.

If shivering does not occur, production of carbon dioxide falls by about 50% with a drop in core temperature to 29 °C (McNicol, 1967). This

combined with an increased solubility of carbon dioxide leads to a fall in the respiratory quotient from 0.82 to 0.65 at a core temperature of 30 °C (Reuler, 1978). As in other clinical conditions, the adequacy of ventilation is determined by the measurement of arterial pCO_2 and if artificial ventilation is necessary, appropriate adjustments in the rate and depth of respiration must be made to avoid hyperventilation and respiratory alkalosis with resulting adverse effects on oxyhemoglobin dissociation and cerebral blood flow. Many patients with accidental hypothermia have a significant respiratory acidosis (McNicol, 1967) because of hypoventilation and respiratory assistance may be necessary in these cases.

Hypoxia is also a significant problem encountered with many patients suffering from accidental hypothermia. This is especially important if the increased oxygen demand of shivering cannot be met and a significant oxygen debt develops. The determination of arterial pO_2 is difficult because of the considerable error encountered when determinations of pO_2 are made at a temperature different from that of the patient. The significance of this can be seen in Table IV indicating the appropriate correction factors for pO_2, pCO_2, and pH when these determinations are made assuming a normal body temperature. Despite these corrections, Nicolas, et al. (1974) reported a series of hypothermic patients where the arterial pO_2 was commonly less than 70 mm Hg and many times less than 50 mm Hg.

Table IV: Effect of body temperature on arterial blood gases

	↑ 1 °C *†	↓ 1 °C *†
pH	↓ .015	↑ .015
PCO_2 (mm Hg)	↑ 4.4%	↓ 4.4%
PO_2 (mm Hg)	↑ 7.2%	↓ 7.2%

* = Change with reference to 37 °C
† %= percent change of the value measured at standard 37 °C

Although the only consistent pulmonary abnormality induced by cold exposure is mild bronchodilatation, other abnormalities may be seen when complicating factors such as a decreased cough reflex, a decrease in ventilation, atelectasis, infection, ventilation perfusion abnormalities and noncardiogenic pulmonary edema are present.

Renal Function. Hypothermia has a depressant effect on most indices of renal function although these are usually transient and return to normal within 24 hours of warming (Rosenfeld, 1963). Despite the abnormalities described below, gross renal function remains adequate in most patients. When core temperature drops to about 28 °C, renal blood flow is reduced up to 50 percent by a combination of hypotension, low cardiac output, high renovascular resistance (Rosenfeld, 1963), and a direct effect of cold. Glomerular filtration rate is usually significantly reduced during hypothermia but quickly returns to normal when rewarming is accomplished. The effects of hypothermia on the renal tubule are complex. Sodium, chloride and glucose transport are depressed resulting in natriuresis and glycosuria. Hydrogen ion excretion is also severely impaired contributing significantly to the observed metabolic acidosis. As temperature falls, the ability of the kidney to conserve water is severely impaired due to decreased sensitivity of the nephron to ADH and a depressed output of ADH from the posterior pituitary. As a result of these changes and the shift of plasma volume from the peripheral to the central circulation, the hypothermic patient frequently excretes a relatively large amount of dilute urine despite a low systemic blood pressure or cardiac output (cold diuresis). On the other hand, oliguria may develop at any time during the development or treatment of hypothermia and usually represents hypovolemia or acute tubular necrosis from rhabdomyolysis, shock or drug overdose.

Electrolytes Serum sodium and chloride concentrations are usually normal in uncomplicated accidental hypothermia. The presence of hyponatremia should suggest a complicating disease process such as myxedema, hypoadrenalism, hypopituitarism, vomiting or diarrhea.

Serum potassium is frequently normal in uncomplicated hypothermia but may be slightly depressed especially if respiratory alkalosis is present (Rittenhouse, 1970). Significant hypokalemia without respiratory alkalosis should suggest coexistent alcoholism or malnutrition. Iatrogenic hypokalemia may be seen after treatment if large amounts of potassium-free or glucose-containing solutions are used. Hyperkalemia is unusual unless associated with renal failure or rhabdomyolysis.

Serum calcium levels are usually normal in hypothermia although cases with hypercalcemia (Dundee, 1964) and hypocalcemia (Rittenhouse, 1970) have been reported. Abnormal levels should suggest rhabdomyolysis, alcoholism, renal failure, volume depletion or malnutrition. Hypophosphatemia has been noted during the recovery phase of hypothermia (Levy, 1980).

Reports of serum magnesium have varied but have a tendency to be slightly low (Johnston, 1974).

Acid-base disturbances are very common in hypothermia. Acute exposure to a cold environment frequently results in hyperventilation with resultant respiratory alkalosis. As hypothermia becomes established, patients generally develop a significant acidosis from carbon dioxide

retention and/or lactate accumulation. Carbon dioxide retention frequently occurs as respiratory rate and tidal volume fall. In the hypothermic patient, any increase in arterial pCO_2 produces a greater fall in pH (Fairley, 1961) than would be anticipated in a euthermic patient due to the temperature dependence of the protein buffering capacity of the blood.

The metabolic acidosis produced during hypothermia is primarily lactic acid. Shivering during the initial phases of hypothermia or during rewarming can create a considerable lactate load especially if tissue hypoxia is present. The amount of oxygen available to hypothermic tissues can be adversely affected by blood viscosity, a leftward shift of the oxyhemoglobin dissociation curve by hypothermia, arterial hypoxia, and perfusion of warm metabolically active tissues by cool blood. The lactic acidosis of hypothermia is also worsened by a decreased ability of the liver to metabolize lactate (Shida, 1977). During rewarming, the metabolic acidosis may worsen significantly presumably due to mobilization of lactic acid from poorly perfused peripheral tissues, an increased production of lactate from shivering muscle, and uneven rewarming techniques.

As hypothermia develops, there appears to be a shift in the distribution of body fluids from the plasma volume to the interstitial and intracellular fluid spaces resulting in a tendency to generalized edema and slight intracellular edema.

Gastrointestinal Tract. As with many other functions, hypothermia depresses the gastrointestinal tract. Acute dilatation of the stomach can be seen and should be anticipated especially in patients who are vomiting and have abdominal distention. Gastric erosions and hemorrhages are very common in hypothermia as is adynamic ileus, colonic dilatation and a generalized decrease in splanchnic blood flow (Hallet, 1954). Although the liver itself may be better able to tolerate hypothermic temperatures (Bernhard, 1955), its ability to utilize glucose and metabolize lactic acid is seriously depressed (Shida, 1977). The excretion and detoxification of some drugs are also depressed during hypothermia (McAllister, 1979) so that appropriate judgements concerning blood levels must be made. Extreme abnormalities in liver function tests are unusual with accidental hypothermia (Duguid, 1961). The association of acute pancreatitis with hypothermia is confusing. Some patients develop severe pancreatitis possible due to ischemia (Savides, 1974), while many times the serum amylase is elevated with no clinical evidence of pancreatitis.

Endocrine System. As core temperature falls, the release of most pituitary hormones (including ACTH and ADH) is depressed with normal function being rapidly restored on rewarming (Fruehan, 1960). However, an increase in peripheral levels of thyroid stimulating hormone has been

reported in some species of animals, human infants acutely exposed to cold, and in adults with chronic hypothermia (Fisher, 1971). Several investigators (Wilson, 1970; Woolf, 1972), however, have reported no rise in thyroid stimulating hormone levels in adults with acute exposure or hypothermia.

With acute exposure to cold temperatures, a rise in serum cortisol levels may occur; but as hypothermia becomes established, a fall in adrenal function proportional to the fall in temperature is seen (Hume, 1958; Hume, 1959). This depression in adrenocortical function is due to a direct effect of cold (Bernhard, 1955) and a decreased sensitivity to ACTH as temperature drops below 32 ^{o}C (Felicetta, 1980). Frequently, however, serum cortisol levels are normal or near normal even with profound hypothermia, presumably due to a temperature sensitive decrease in metabolism and conjugation of this hormone by the liver. The depression of adrenal responsiveness to ACTH rapidly returns to normal after rewarming (Felicetta, 1980).

The response of the adrenal medulla to hypothermia is biphasic. Initially a rise in serum epinephrine and norepinephrine (Arnett, 1960) occurs as a response to thermoregulatory and environmental stress. Elevated urinary catecholamines have also been reported in persons who died from hypothermia (Hirvonen, 1982). As temperature approaches 30 ^{o}C, however, catecholamines begin to fall (Hume, 1958) with a significant depression occurring by 28 ^{o}C (Wood, 1980). At any temperature below normal, the serum levels of catecholamines may not accurately reflect adrenal release because of a decrease in activity of catechol o-methyl transferase and monoamine oxidase (Schneider, 1966).

Acutely, no change is seen in serum thyroxine levels after up to three hours of exposure to cold (Wilson, 1970) although a decrease in temperature of 2 ^{o}C may decrease free T4 by 25 percent. Although thyroid sensitivity to TSH is depressed, the long half-life of thyroxine prevents any significant change in the levels of this hormone during acute hypothermia, and the development of significant hypothyroidism is unlikely unless exposure is severe and prolonged.

Hypothermia results in a reversible depression of the pancreas with a fall in insulin release due most likely to a direct effect of cooling and not alpha adrenergic stimulation (Curry, 1970; Shida, 1981). This inadequate insulin response is illustrated in Figure 20.

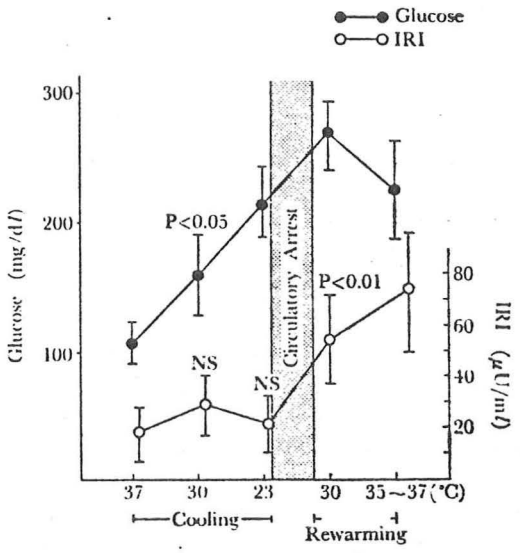


Figure 20. Changes of blood glucose and plasma IRI during hypothermic open-heart surgery (Shida, 1981)

Peripheral glucose utilization is also depressed (Fruehan, 1960; Landymore, 1979) and resistant to large amounts of insulin. Hyperglycemia is commonly encountered in hypothermia and can be quite severe. The causes of this rise in glucose include: 1) inadequate insulin, 2) depressed peripheral utilization of glucose, 3) increased glycogenolysis and 4) increased catecholamines early with exposure.

An increase in free fatty acid levels is seen early with exposure and persists with the development of hypothermia. These compounds are an important energy source for shivering muscles and are produced probably in response to sympathetic stimulation (Nesbakken, 1973). It has been suggested that these compounds may contribute to myocardial toxicity in ischemic situations (Opie, 1974) but their relevance to arrhythmias in hypothermia is unknown.

Hematologic System. The cold diuresis and fluid compartment shifts that occur with hypothermia create a variable amount of hemoconcentration (Duguid, 1961; Prescott, 1962) and a fall in plasma volume (Chen, 1980). However, the extent of hemoconcentration is variable as shown in the study of White (1982) where the mean hematocrit was 33.6 percent. The white cell count, on the other hand, usually falls as temperature drops to 32 ^{o}C and can be severe if temperature is less than 28 ^{o}C. The white cell differential count is usually normal (Duguid, 1961) as is the white cell response to infection with moderate degrees of hypothermia (Blair, 1969). Some degree of thrombocytopenia is common although severe depressions in platelet count are usually seen only with temperatures less than 30 ^{o}C. Disseminated intravascular coagulation can be seen with rewarming (Mahajan, 1981).

Factors Associated or Predisposing to Hypothermia

Severe hypothermia is unusual in young healthy persons except in situations of severe cold stress. Most patients seen in metropolitan hospitals suffer from some underlying illness or disorder which predisposes them to the development of hypothermia (White, 1982). Identification of these predisposing factors and conditions is necessary for treatment as well as prevention of hypothermia. While a detailed discussion of these disorders is not possible in this presentation, some of the more important predisposing conditions will be addressed.

Elderly. The elderly are particularly susceptible to the effects of low environmental temperature. Like classic heat stroke, hypothermia in the elderly occurs mostly indoors and in combination with significant medical illness. Fixed income, substandard housing, poor insulation and mechanical problems with heating sources combine to allow the nighttime bedroom temperatures of many old people to approach that of the outside environment. Studies have shown that elderly persons with cold homes tend to have lower oral as well as early morning urine temperatures (Fox, 1973). Advancing age, receiving supplemental benefits, a perception of cold extremities and a preference for a warmer environment are all associated with a low morning temperature in elderly patients.

Thermoregulatory responses diminish progressively with age (Collins, 1977) due to a combination of factors including:

1) decreased vasoconstrictor response when exposed to a cool environment (Wagner, 1974) decreasing the ability to conserve heat (Lee, 1965)

2) decreased ability to generate heat by metabolic processes (Wagner, 1974) and shivering.

3) malnutrition (Murphy, 1963) and a decrease in subcutaneous fat

4) possible decreased sensitivity to the thermal discomforts of cold (Watts, 1972).

The mortality rate for hypothermic elderly patients is high (Irvine, 1973; Bristow, 1977) primarily because of the high incidence of severe coexisting medical illness (Hudson, 1974; Bristow, 1977; White, 1982).

Metabolic. Several endocrinopathies can present as or have hypothermia as a complicating factor. Probably the most widely recognized of these is hypothyroidism although the incidence of this disorder in hypothermic patients is probably less than 10 percent (Hudson, 1974; Fischbeck, 1981; White, 1982). In severe hypothyroidism, metabolic heat production can be severely depressed because of low thyroxine levels, and most patients have low body temperatures. However, bradycardia, atrial fibrillation, cardiomegaly, edema, myxedematous facies, mental slowing and delayed relaxation of the deep tendon reflexes (Maclean, 1973) can

be seen with uncomplicated hypothermia and mimic hypothyroidism. Patients with concomitant hypothermia and myxedema have a very high mortality. The development of hypothermia in a myxedematous person, especially in a warm environment should suggest infection, drug use (especially sedatives), or trauma. Hypoglycemia frequently presents with hypothermia probably due to a central nervous system deprivation of glucose (Freinkel, 1972). Hypopituitarism may also present with hypothermia and coma, especially in concert with infection or volume depletion. Other signs of hypopituitarism should suggest the diagnosis and treatment should include volume repletion, corticosteroids and glucose as well as rapid rewarming. Diabetes mellitus with ketoacidosis can present with hypothermia and may be a more frequent cause than hypothyroidism (Gale, 1978) especially during warmer months.

Central Nervous System Disease. Many central nervous system disorders can present with hypothermia. Many of these, as expected, involve the hypothalamus, although more generalized cerebral conditions and disruption of afferent and efferent thermoregulatory tracts can result in significant loss of temperature control. The list of central nervous system conditions associated with hypothermia is extensive and includes: cerebrovascular disease, subdural hematoma, tumors, head trauma, anorexia nervosa, Shapiro's syndrome, Parkinson's disease, Wernicke's encephalopathy, spinal cord transection, sarcoidosis, Alzheimer's disease, and schizophrenia. A syndrome of recurrent spontaneous hypothermia similar to Shapiro's syndrome, but without definable neurologic pathology, has been described in several patients (Duff, 1961; Slotki, 1980).

Drugs. Many drugs in therapeutic and supratherapeutic doses can influence the body's ability to regulate temperature. Alcohol is probably the most common drug encountered in this group. Patients are usually chronic alcoholics subject to chronic exposure to cold environments although alcohol can significantly impair thermoregulation in young, healthy persons (Graham, 1980). Vasodilation, reduced shivering, decreased central thermoregulatory sensitivity, exposure, impaired judgement, hypoglycemia (Fitzgerald, 1980), and Wernicke's encephalopathy (Macaron, 1979; Donnan, 1980) contribute to the hypothermic predisposition of alcohol. As with other causes of drug induced hypothermia, mortality increases with the presence of other underlying diseases (Weyman, 1974).

In therapeutic doses, many drugs counteract thermoregulatory responses and predispose to hypothermia. These drugs are especially dangerous to patients with other medical illnesses which predispose to thermoregulatory failure and include: phenothiazines, tricyclic antidepressants, benzodiazepines, morphine, reserpine, general anesthetics and possibly lithium carbonate and prazosin (Naylor, 1977; De Leeuw, 1980).

Other drugs usually require supratherapeutic doses (usually overdose) to seriously impair thermoregulation and cause hypothermia. These include: barbiturates, glutethimide, meprobamate, methaqualone, ethchlorvynol, heroin, cannabis, and ethylene glycol. Interestingly, the prognosis for most of these overdoses with hypothermia is better than for other predisposing causes.

Malnutrition. Malnutrition can seriously impair the body's ability to cope with a cold environment. This is especially important in the elderly, vagrants, children with protein calorie malnutrition and those with anemia of nutritional origin.

Dermal Dysfunction. Generalized erythrodermal skin diseases are occasionally associated with hypothermia (Grice, 1967); Cucinell, 1978) due to an increased cutaneous blood flow and evaporative heat loss. For the same reasons, burn patients are also predisposed to hypothermia.

Paget's Disease of Bone. Hypothermia can develop in patients with Paget's disease of bone because of the increased vascularity of bony areas resulting in increased heat loss.

Exposure. Obviously, severe cold stress can lead to hypothermia in any individual but certain conditions make its development more likely. For example, immersion in cold water results in a greater loss of heat than exposure to air of equal temperature because of the high thermal conductance of water. Immersion in water 10 - 15 ^{o}C usually leads to uncontrollable gasping and swimming is possible for only a short distance (Goode, 1975; Hayward, 1975). Heat loss in this situation is facilitated by movement and can be minimized by flexing the arms to the axilla and legs to the abdomen. Recent studies have suggested that men working underwater may develop significant hypothermia without symptoms (Hayward, 1979; Keatinge, 1980). This was most likely to occur in those with little subcutaneous fat. Marcus (1979) has also demonstrated that cold discomfort is inversely proportional to work rate. Authors have reported that hypothermia can also develop in temperate climates, especially in elderly patients with concurrent medical illness (Altus, 1980).

In summary, numerous clinical situations impair thermoregulatory function and predispose to hypothermia. In general, those related to drug or toxin overdose and environmental exposure without underlying medical illness have a much better prognosis. A summary of these conditions is outlined in Table V.

Table V: Clinical Associations with hypothermia (Duguid, 1961; McNicol, 1964; Hudson, 1974; Reuler, 1978; Whittle, 1979; Fischbeck, 1981; White, 1982)

Elderly

Metabolic Diseases

- Hypothyroidism
- Diabetic ketoacidosis
- Renal failure
- Hypoglycemia
- Hypopituitarism
- Hypoadrenalism
- Hepatic encephalopathy

Central Nervous System Diseases

- Cerebrovascular disease
- Subdural hematoma
- Tumors
- Head trauma
- Anorexia nervosa
- Shapiro's syndrome
- Parkinson's disease
- Wernicke's encephalopathy
- Spinal cord transection
- Sarcoidosis
- Alzheimer's disease
- Schizophrenia
- Recurrent spontaneous hypothermia
- Hypothalamic gliosis

Drugs

- <u>Therapeutic Levels</u>
- Ethanol
- Phenothiazines
- Tricyclic antidepressants
- Benzodiazepines
- Morphine
- Reserpine
- Generalized anesthesia
- ? Lithium + Benzodiazepines
- ? Prazosin

Table V (continued):

Drugs

Suprathérapeutic Levels (overdoses)
Barbiturates
Carbon monoxide
Glutethimide
Meprobamate
Methaqualone
Ethchlorvynol
Heroin
Cannabis
Ethylene glycol
Organophosphates

Malnutrition

Dermal Dysfunction

Paget's Disease of Bone

Infections

Gram negative bacteremia
Gram positive bacteremia
Tuberculosis
Peritonitis
Meningitis

Pancreatitis

Shock

Myocardial infarction
Congestive heart failure
Gastrointestinal bleeding

Exposure

Management of Hypothermia

Hypothermia is defined as a core temperature of less than 35 ^{o}C and should be considered a medical emergency. Most routine emergency room thermometers do not measure temperatures below about 34.5 ^{o}C, so the diagnosis of hypothermia depends largely on a high index of suspicion. If the diagnosis is being entertained, an estimate of core temperature should be obtained by one of several means. A high rectal temperature obtained with a thermistor probe will give a reasonable measurement of core temperature in most patients. Esophageal temperature with the probe placed at the level of the right atrium will perhaps give a more accurate measurement of core temperature, but such measurements are uncomfortable to the patient, difficult to properly place, and may precipitate ventricular arrhythmias or fibrillation. The tympanic membrane is supplied by a branch of the carotid artery, as is the hypothalamus, and may be used to estimate core temperature if an appropriate instrument is available. All things considered, rectal temperature is probably the most frequently used.

Once the diagnosis has been made, any predisposing causes or complications of hypothermia should be sought with a thorough history and physical examination because mortality is directly related to their presence. If the patient is comatose, steps must obviously be taken to insure an adequate airway and prevent gastric aspiration. A large intravenous catheter should be inserted and thiamine given immediately. Stimulation of the patient, however, should be kept to a minimum to avoid precipitating ventricular fibrillation. A chest X-ray should be obtained to detect complicating factors such as pneumonia, aspiration, congestive heart failure or adult respiratory distress syndrome. Abdominal X-rays should be obtained if there is any evidence of gastric or colonic dilatation, peritonitis, ileus, pancreatitis or gastrointestinal hemorrhage. Hematologic evaluation should be directed towards identifying predisposing causes as well as complications of hypothermia. Suggested laboratory evaluation is outlined in Table VI.

Table VI: Laboratory evaluation of hypothermia

All Patients	Selected Patients
Complete Blood Count	Serum Lactate
Platelets	Serum Ketones
Glucose	Toxicology Screen
BUN/Creatinine	Carboxyhemoglobin
Sodium	Calcium and Magnesium
Potassium	Inorganic Phosphate
Chloride	Cortisol
Bicarbonate	Thyroxine
Amylase	CPK
Arterial pH, pCO_2, pO_2	
Urinalysis	
Prothrombin Time	
Partial Thromboplastin Time	

While a low or low normal white blood cell count is expected in significant hypothermia, one must not ignore the possible contribution of coexistent malnutrition or folate deficiency. An elevated white blood cell count, especially with a left shift should suggest an underlying infection. The platelet count is also depressed by hypothermia, but again complicating folate deficiency or disseminated intravascular coagulation should be considered. An elevated hemoglobin is common in hypothermia and suggests hemoconcentration due to volume depletion or fluid compartment shifts. A low hemoglobin may be seen if gastrointestinal bleeding, malnutrition, alcoholism or folate deficiency is present. Hyperglycemia due to increased glycogenolysis, poor peripheral utilization of glucose and inadequate insulin release is frequently encountered. Hypoglycemia on presentation should suggest concurrent alcoholism or diabetes mellitus.

A serum amylase should be measured on all patients because of the association of hypothermia with pancreatitis. Arterial pH measurement is necessary because metabolic and respiratory acidosis may be life threatening. Hypoxia should suggest underlying pulmonary pathology such as pneumonia or adult respiratory distress syndrome. Hypercarbia is frequently seen in uncomplicated hypothermia, but its presence in the appropriate situation should suggest hypothyroidism. A low arterial pCO_2 usually indicates a complication such as pneumonia, lactic acidosis, or diabetic ketoacidosis is present. Arterial blood gas measurements should be corrected for body temperature (Table IV). Serum lactate and ketones should be measured in patients who have a serious metabolic acidosis. Toxicologic evaluation is indicated in any patient whose history is unknown or if the possibility of drug or poison ingestion exists. Calcium, magnesium, and inorganic phosphate measurements are important in alcoholic patients and in those with myoclonus or rhabdomyolysis. Serum cortisol and thyroxine levels are warranted if the clinical situation suggests hypothyroidism, adrenal insufficiency or hypopituitarism. Creatine kinase may be elevated in patients with rhabdomyolysis or hypothyroidism.

Constant electrocardiographic monitoring is mandatory for all patients during rewarming because of the significant incidence of arrhythmias and ventricular fibrillation. Late rewarming collapse due to severe bradycardia or heart block can occur up to 48 - 72 hours after rewarming and should be treated with a pacemaker if necessary. Blood pressure, pulse, temperature, neurologic status and urine output should be monitored frequently during rewarming. Central venous and arterial pressure monitoring, Swan-Ganz catheterization, and cardiac pacing may be necessary in selected patients. Swan-Ganz catheterization and cardiac pacing should be avoided if possible because the irritation can precipitate ventricular fibrillation in the hypothermic myocardium.

Rewarming techniques. The proper technique for rewarming hypothermic patients has become a subject of considerably controversy. General recommendations regarding the treatment of hypothermia are difficult to establish because of the wide variety of predisposing factors and

complicating diseases. However, certain considerations should influence the method of rewarming chosen for a given patient. It has long been accepted that a warming rate of about 0.55 °C per hour is optimal although many shivering young persons may produce heat at a much faster rate. Consequently, many authorities believe that passive rewarming of hemodynamically stable hypothermic patients is best. With this technique, the patient is allowed to generate his own heat with insulating material such as blankets being the only external intervention. In general, this method will allow a slow rise of 0.5 - 1.0 °C/hour in most patients if the initial core temperature is greater than about 27 °C (Cooper, 1960). If the increase in temperature is less than 0.5 ° per hour, a complicating disease such as hypothyroidism should be suspected. This passive method of rewarming is especially effective in patients with acute hypothermia without significant underlying disease. Although this method has been used successfully by many authorities (Gregory, 1973), mortality may still be high (Fruehan, 1960; Duguid, 1961; Prescott, 1962).

Active rewarming methods have been advocated by some as a means to rapidly return core temperature to near normal in patients with severe hypothermia and/or cardiorespiratory arrest. The fibrillating hypothermic myocardium is resistant to mechanical or pharmacologic intervention until temperatures are above 28 - 30 °C (Linton, 1966). For this reason, no hypothermic person should be pronounced dead until the core temperature is above 30 °C. DaVee (1980) has reported a patient with functional survival after a fall in core temperature to 16 °C and prolonged cardiopulmonary resuscitation. Successful resuscitation after cardiac arrest with hypothermia generally depends on a previously healthy heart and the protective effects of hypothermia.

Several disadvantages of active rewarming have been described. "Rewarming shock" occurs when rewarming causes a decrease in the intense vasoconstriction resulting in a fall in peripheral vascular resistance and blood pressure if the cardiac output cannot be increased. This is especially a problem in elderly persons with significant preexisting cardiovascular disease (Duguid, 1961). When patients are actively heated externally, a drop in core temperature is occasionally seen before rewarming begins. This fall in core temperature has been implicated in precipitating ventricular fibrillation during the early phases of treatment. This "after drop" in core temperature was thought to be due to cold blood in peripheral tissues being returned to the central circulation by vasodilatation induced by rewarming, although it may be due in part to the delayed conduction of heat from the external to internal environment. Finally, the lactic acidosis associated with hypothermia may be worsened significantly with active rewarming because of uneven rewarming and renewed perfusion of ischemic tissues.

Active rewarming generally is divided into external and internal techniques. With active external rewarming, heat is applied to the surface of the body with hot water bottles, warm water, etc. This method of rewarming has been used most successfully in young patients

with acute hypothermia (Bristow, 1977). External rewarming, however, is more likely to induce "rewarming shock", especially in older persons with chronic exposure (Duguid, 1961). The success of active rewarming has been varied. Duguid (1961) and Weyman (1974) have reported an increased mortality in patients rewarmed by active methods. However, Frank (1980) reported ten patients, seven of which had underlying medical problems, who were successfully treated by immersion into a 40 ^{o}C water bath despite the fact that some of the patients were elderly.

To avoid the above problems with active external rewarming, rapid rewarming of core blood has been attempted by several means. This active core rewarming minimizes rewarming shock and acidosis and avoids afterdrop of core temperature. Methods used to accomplish active core rewarming are summarized in the following table.

Table VII: Core rewarming techniques

Heart lung machine with heat exchanger (Kugelberg, 1967; Fell, 1968; Towne, 1972; Truscott, 1973; Althaus, 1982)
Hemodialysis
Heated oxygen (Lloyd, 1973; Hayward, 1975; Collis, 1977; Harnett, 1980; Morrison, 1980)
Peritoneal lavage (Lash, 1967; Pickering, 1977; Jessen, 1978)
Mediastinal lavage (Linton, 1966; Althaus, 1982)
Warm gastric lavage (Ledingham, 1980a)
Colonic lavage
Warm IV solutions
Radiant heat cradle over torso (Ledingham, 1980b)
Microwave (Westenskow, 1979)

In summary, the method of rewarming will depend in large part on the patient and the necessity for rapid rewarming. In general, young patients with acute immersion hypothermia will rewarm rapidly with passive techniques if hypothermia is not extreme. Active external rewarming should be avoided in older patients with relatively chronic hypothermia and significant underlying cardiovascular disease. Patients with cardiopulmonary arrest should be rapidly rewarmed by a core rewarming technique to at least 30 ^{o}C while resuscitative measures are in progress. Mortality by any technique depends primarily on the presence or absence of underlying diseases. If the patient is healthy, any rewarming technique will be successful (Tafari, 1974); and if serious underlying diseases are present, mortality will be high no matter how the patient is warmed (Hudson, 1974). To date, there are no controlled, randomized studies comparing the above rewarming techniques.

Oxygen. Hypothermia decreases the metabolic requirements of the body, but the adverse effects temperature has on the oxygen dissociation curve

may cause an inadequate amount of oxygen to be delivered to peripheral tissues. If the corrected arterial pO_2 is normal, enough oxygen is probably available to meet the metabolic demand. However, if hypoxia develops, significant tissue injury and metabolic acidosis will result. Shivering during rewarming may greatly increase the oxygen requirement by muscle and worsen the metabolic acidosis if oxygen supply is inadequate. Because of these factors, hypothermic patients should be given supplemental oxygen with ventilatory assistance if necessary.

Fluid and Electrolytes. No general recommendation regarding the fluid and electrolyte requirements of hypothermic patients can be given because of their wide diversity. Any intravenous fluid that is given should be warmed to 37 to 40 ^{o}C before administration. This can easily be accomplished with a blood warmer. Many patients will require central venous pressure monitoring to accurately determine their volume requirements. Rewarming shock should be treated vigorously by expanding plasma volume if the central venous pressure is low.

Dehydration can be determined by measuring osmolality or estimated from the serum sodium and usually occurs in patients who have an inability to drink water or have an altered hypothalamic thirst mechanism. If significant dehydration is present, careful repletion with free water in the form of D_5W is indicated. However, one must keep in mind that fluid compartment shifts with rewarming will correct some of the elevated serum osmolality. Sodium depletion should be determined clinically and correction undertaken if indicated to improve tissue perfusion (Suzuki, 1966). Volume overload, however, should be carefully avoided.

Acid-base disturbances. The ideal pH and arterial pCO_2 in patients with hypothermia are not known, but values should probably be near normal to maximize ventricular function and vascular responsiveness, prevent respiratory depression and allow catecholamines and drugs to function predictably. As noted above, these values should be corrected for body temperature if the measurements are made assuming a temperature of 37 ^{o}C. Bicarbonate should be given for serious metabolic acidosis (pH less than 7.2), but care must be exercised to avoid subsequent metabolic alkalosis and its adverse effects on oxyhemoglobin dissociation, calcium, ventricular irritability, and cerebral blood flow. With rewarming, a transient worsening of the metabolic acidosis may occur as tissue hypoxia develops and lactate is washed out of previously vasoconstricted tissues. Recognition and treatment of this phenomenon is important to reduce the risk of ventricular fibrillation. A mild respiratory acidosis may favorably affect oxygen delivery and counteract intense peripheral vasoconstriction, but severe respiratory impairment with significant carbon dioxide retention should be treated with assisted ventilation. Again, alkalosis should be avoided by appropriate ventilatory adjustments realizing the reduced carbon dioxide generation in hypothermic patients.

Glucose. Hypoglycemia should obviously be suspected in any patient presenting with hypothermia. On the other hand, hyperglycemia should be treated only if severe and potentially life threatening. Insulin has little effect if the core temperature is below 30 °C and if given, serious hypoglycemia and hypokalemia can result as rewarming takes place. Diabetic ketoacidosis with serious hypothermia (below 30 °C) is probably an indication for rapid rewarming so that exogenous insulin can exert its metabolic effect.

Steroids. Convincing data supporting the routine use of corticosteroids in hypothermic patients does not exist, and Stoner (1980) has indicated that circulating cortisol levels are adequate in hypothermic patients. Some authorities advocate the use of high dose corticosteroids in these patients on the theoretical grounds that they increase coronary blood flow, decrease the oxygen consumption of the myocardium (La Croix, 1958), shift the oxyhemoglobin dissociation curve to the right (McConn, 1971), stabilize lysosomal membranes, and preserve myocardial function in hyperkalemic hypothermic cardioplegia (Levinsky, 1979). In summary, until convincing data are available, corticosteroids probably should not be used unless adrenal or pituitary insufficiency or hypothyroidism is suspected.

Vasopressors. In general, vasopressors should be avoided if possible because of their ability to induce ventricular arrhythmias in hypothermic patients. Hypotension should be first treated with volume and plasma expansion as indicated by measurements of central venous pressure or pulmonary capillary wedge pressure.

Antiarrhythmic drugs. Drugs with significant myocardial depressing effects such as quinidine and propranolol should be avoided in hypothermia because of their propensity to depress cardiac output and worsen hypotension.

Antibiotics. Data supporting the routine use of prophylactic antibiotics in hypothermia do not exist, and one should withhold these drugs until specific indications exist.

Thyroxine. Thyroxine should be given if significant hypothyroidism is suspected. Replacement doses of corticosteroids probably should also be given with this drug.

To conclude, accidental hypothermia is a medical emergency with mortality directly related to the presence of serious underlying disease. Supportive measures and rewarming techniques must be individualized but usually involve passive or active internal methods.

Treatment of concomitant underlying illnesses is important if significant survival is to be anticipated.

REFERENCES

Abbott TR (1977) Oxygen uptake following deep hypothermia. Anaesthesia 32:524.

Adolph EF (1950) Oxygen consumption of hypothermic rats and acclimitization to cold. Amer J Physiol 161:359.

Althaus U, Aeberhard P, et al. (1982) Management of profound accidental hypothermia with cardiorespiratory arrest. Ann Surg 195:492.

Altus P, Hickman JW, et al. (1980) Hypothermia in the sunny south. South Med J 73:1491.

Andrews C and Orkin LR (1964) Environmental cold and man. Anesthesiology 25:549.

Arnett EL and Watts DL (1960) Catecholamine excretion in men exposed to cold. J Appl Physiol 15:499.

Barboax HG (1921) The heat regulating mechanism of the body. Physiol Rev 1:295.

Baum D, Dillard DH, and Porte D (1968) Inhibition of insulin release in infants undergoing deep hypothermic cardiovascular surgery. N Engl J Med 279:1309.

Benzinger TH, Kitzinger C, Pratt AW. (1963) The human thermostat. In Temperature: Its Measurement and Control in Science and Industry. (Editor: JD Hardy),

Bernard C (1876) Lecons sur la Chaleur Animale. Balliere, Paris.

Bernhard WF, McMurrey JD and Curtis GW (1955) Feasibility of partial hepatic resuscitation under hypothermia. N Engl J Med 253:154.

Bernhard WF and McMurrey JD (1955) Inhibition of the stress response during surgery under hypothermia. Surg Forum 6:146

Bernhard WF, Schwartz HF and Mallick NP (1960) Intermittent cold coronary perfusion as an adjunct to open-heart surgery. Surg Gynecol Obstet 111:744.

Berne RM (1953) Myocardial function in severe hypothermia. Circ Res 2:90.

Berne RM (1954) The effect of immersion hypothermia on coronary blood flow. Circ Res 2:236

Berne RM (1959) Cardiodynamics and the coronary circulation in hypothermia. Ann NY Acad Sci 80:365.

Bigelow WG, Lindsay WK, et al. (1950) Oxygen transport and utilization in dogs at low body temperatures. Amer J Physiol 160:125.

Blair E, Esmond WG, et al. (1964) The effect of hypothermia on lung function. Ann Surg 160:814.

Blair E (1965) Physiologic classification of clinical hypothermia. Surgery 58:607.

Blair E (1969) Physiologic and metabolic effects of hypothermia in man in Depressed Metabolism. Proceedings of the First International Conference on Depressed Metabolism, Washington D.C., August 22-23, 1968. Ed. Musacchia XJ and Saunders JF, American Elsevier, New York.

Boulant JA (1974) The effect of firing rate on preoptic neuronal thermosensitivity. J Physiol (London) 215:1151.

Bradley AF, Stupfel M, Severinghaus JW (1956) Effect of temperature on PCO_2 and PO_2 of blood in vitro. J Appl Physiol 9:201.

Bristow G, Smith R, et al. (1977) Resuscitation from cardiopulmonary arrest during accidental hypothermia due to exhaustion and exposure. Can Med Assoc J 117:247.

Brodie B (1812) Further experiments and observations on the influence of the brain on the generation of animal heat. Philos Trans R Soc London (Biol) 378.

Carlson CJ, Emilson B, and Rapaport E (1978) Creatine phosphokinase MB isoenzyme in hypothermia: Case reports and experimental studies. Am Heart J 95:352.

Chen RYZ, Wicks AE and Chien S (1980) Hemoconcentration induced by surface hypothermia in infants. J Thorac Cardiovasc Surg 80:236.

Clarkson PM, MacArthur BA, et al. (1980) Developmental progress after cardiac surgery in infancy using hypothermia and circulatory arrest. Circulation 62:855.

Cohen ME, Olszowka JS and Subramian S (1977) Electroencephalographic and neurological correlates of deep hypothermia and circulatory arrest in infants. Ann Thorac Surg 23:238.

Collins KJ, Dore C, et al. (1977) Accidental hypothermia and impaired temperature homeostasis in the elderly. Br Med J 1:353.

Collis ML, Steinman AM and Chaney RD (1977) Accidental hypothermia: an experimental study of practical rewarming methods. Aviat Space Environ Med 48:625.

Cucinell SA (1978) Hypothermia and generalized skin disease (letter). Arch Dermatol 114:1244.

Currie J (1805) Medical Reports on the Effects of Water, Cold and Warm as a Remedy in Fever and Other Diseases, Vol. I. Cadell and Davies, London.

Curry DL and Curry KP (1970) Hypothermia and insulin secretion. Endocrinology 87:750.

DaVee TS and Reineberg EJ (1980) Extreme hypothermia and ventricular fibrillation. Ann Emer Med 9:100.

De Leeuw PW and Birkenhager WH (1980) Hypothermia: a possible side effect of prazosin. Br Med J 281:1181.

Derbyshire DR and Clark RG (1980) Cerebral recovery after prolonged global brain ischaemia. Lancet 2:637.

Donnan GA and Seeman E (1980) Coma and hypothermia in Wernicke's encephalopathy. Aust NZ J Med 10:438.

Drake CE and Flowers NC (1980) EKG changes from sepsis and unrelated to exposure. Chest 77:685.

Duff RS, Farrant PC, et al. (1961) Spontaneous periodic hypothermia. Quart J Med 30:329.

Duguid H, Simpson RG and Stowers JM (1961) Accidental hypothermia. Lancet 2:1213.

Dundee JW and Clark RSJ (1964) Pharmacology of hypothermia. Int Anesth Clin 2:857.

Edwards WF (1832) On the Influence of Physical Agents on Life. Highly, London.

Ehrmantraut WR, Ticktin HE and Fazekas JF (1957) Cerebral hemodynamics and metabolism in accidental hypothermia. AMA Arch Intern Med 99:57-59.

Exton-Smith AN (1973) Accidental hypothermia. Br Med J 4:727

Fairley HB (1961) Metabolism in hypothermia. Br Med Bull 17:52.

Falk RB, Denlinger JK and O'Neill MJ (1977) Changes in the electrocardiogram associated with intraoperative epicardial hypothermia. Anesthesiology 46:302.

Felicetta JV, Green WL and Goodner CJ (1980) Decreased adrenal responsiveness in hypothermic patients. J Clin Endocrinol Metab 50:93.

Fell RM, Gunning AJ, et al. (1968) Severe hypothermia as a result of barbiturate overdose complicated by cardiac arrest. Lancet 1:392.

Fischbeck KH and Simon RP (1981) Neurological manifestations of accidental hypothermia. Ann Neurol 10:384.

Fisher DA and Odell WD (1971) Effect of cold on TSH secretion in man. J Clin Endocrinol Metab 33:859.

Fisher A, Foëx P, et al. (1977) Oxygen availability during hypothermic cardiopulmonary bypass. Crit Care Med 5:154.

Fitzgerald FT (1980) Hypoglycemia and accidental hypothermia in an alcoholic population. West J Med 133:105.

Fox RH, Woodward PM, et al. (1973) Body temperatures in the elderly: a national study of physiological, social, and environmental conditions. Br Med J 1:200.

Frank DH and Robson MC (1980) Accidental hypothermia treated without mortality. Surg Gynecol Obstet 151:379.

Freinkel N, Metzger BE, et al. (1972) The hypothermia of hypoglycemia. N Engl J Med 287:841.

Fruehan AE (1960) Accidental hypothermia. Arch Intern Med 106:218.

Gale EAM and Tattersall RB (1978) Hypothermia: a complication of diabetic ketoacidosis. Br Med J 2:1387.

Goode RC, Duffin J, et al. (1975) Sudden cold water immersion. Respir Physiol 23:301.

Goodyer AVN (1965) Effects of hypothermia and pyrexia on left ventricular function in the intact animal. Amer J Cardiol 15:206.

Grice KA and Bettley FR (1967) Skin water loss and accidental hypothermia in psoriasis, ichthyosis and erythroderma. Br Med J 4:195, 1967.

Graham T and Baulk K (1980) Effect of alcohol ingestion on man's thermoregulatory responses during cold water immersion. Aviat Space Environ Med 51:155.

Gregory RT and Doolittle WH (1973) Accidental hypothermia. Part II: Clinical implications of experimental studies. Alaska Med 15:48.

Gunton RW and Scott JW, et al. (1956) Changes in cardiac rhythm and in the form of the electrocardiogram resulting from induced hypothermia in man. Am Heart J 52:419.

Haka-Ikse K, Blackwood MJA and Steward DJ (1978) Psychomotor development of infants and children after profound hypothermia during surgery for congenital heart disease. Dev Med Child Neurol 20:62.

Hallet EB (1954) The effect of decreased body temperature on liver function and splanchnic blood flow in dogs. S Forum 5:362.

Harnett RM, O'Brien EM, et al. (1980) Initial treatment of profound accidental hypothermia. Aviat Space Environ Med 51:680.

Hayward JS, Eckerson JD and Collis ML (1975) Effect of behavioral variables on cooling rate of man in cold water. J Appl Physiol 38:1073.

Hayward JS and Steinman AM (1975) Accidental hypothermia: an experimental study of inhalation rewarming. Aviat Space Environ Med 46:1236.

Hayward MG, and Keatinge WR (1979) Progressive symptomless hypothermia in water; possible cause of diving accidents. Br Med J 1:1182.

Hensel H (1952) Physiologie der thermoreception. Ergebn Physiol 47:166.

Hensel H (1970) Temperature receptors in the skin. In Physiological and Behavioral Temperature Regulation (Editors: JD Hardy, AP Gagge, JAJ Stolwijk), Charles C. Thomas, Springfield, Illinois, p 442.

Hensel H, Andres KH and Düring M (1974) Structure and function of cold receptors. Pfluegers Arch 352:1.

Hervey GR (1973) Physiological changes encountered in hypothermia. Proc R Soc Med 66:1053.

Hirvonen J and Huttunen P (1982) Increased urinary concentrations of catecholamines in hypothermic deaths. J Forensic Sci 27:264.

Horvath SM, Hutt BK, et al. (1953) Some metabolic responses of dogs having low body temperature. Science 118:100.

Hudson LD and Conn RD (1974) Accidental hypothermia. Associated diagnoses and prognosis in a common problem. JAMA 227:37.

Hume DM and Bell CC 1958) The secretion of epinephrine, norepinephrine, and corticosteroid in the adrenal venous blood of the human. Surg Forum 9:6.

Hume DM and Egdahl RH (1959) Effect of hypothermia and of cold exposure on adrenal cortical and medullary secretion. Ann NY Acad Sci 80:435.

Iggo A (1969) Cutaneous thermoreceptors in primates and subprimates. J Physiol (London) 115:1129.

Irvine RE (1973) Hypothermia. Mod Geriat 3:464.

Ivy AC (1944) What is normal or normality? Quart Bull Northwestern Univ Med Schl 18:22.

Jacob AI, Lichstein E, et al. (1978) A-V block in accidental hypothermia. J Electrocardiol 11:399.

Jessen K and Hagelsten J (1978) Peritoneal dialysis in the treatment of profound accidental hypothermia. Aviat Space Environ Med 49:426.

Johnston AE, Radde IC, et al. (1974) Acid-base and electrolyte changes in infants undergoing profound hypothermia for surgical correction of congenital heart disease. Can Anaesth Soc J 21:23.

Kanter GS (1968) Hypothermic hemoconcentration. Am J Physiol 214:856.

Keatinge WR, Hayward MG and McIver MKI (1980) Hypothermia during saturation diving in the North Sea. Br Med J 280:291.

Kelman GR and Nunn JF (1966) Nomograms for correction of blood PO_2, PCO_2, pH, and base excess for time and temperature. J Appl Physiol 21:1484.

Kugelberg J, Schüller H, et al. (1967) Treatment of accidental hypothermia. Scand J Thorac Cardiovasc Surg 1:142.

Kuhn LA and Turner JK (1959) Alterations in pulmonary and peripheral vascular resistance in immersion hypothermia Circ Res 7:366.

LaCroix E and Leusen I (1958) The influence of cortisone on the oxygen consumption of myocardial and diaphragmatic slices in the rat. Arch Int Pharmacodyn Ther 114:103.

Landymore RW, Murphy DA and Longley WJ (1979) Effect of cardiopulmonary bypass and hypothermia on pancreatic endocrine function and peripheral utilization of glucose. Can J Surg 22:248.

Lash RF, Burdette JA and Ozdil T (1967). Accidental profound hypothermia and barbiturate intoxication. A report of rapid "core" rewarming by peritoneal dialysis. JAMA 201:267.

Ledingham IM, Routh GS, et al. (1980a) Central rewarming system for treatment of hypothermia. Lancet 1:1168.

Ledingham IM and Mone JG (1980b) Treatment of accidental hypothermia: a prospective clinical study. Br Med J 280:1102.

Lee DY, Hong SK and Lee PH. (1965) Physical insulation of healthy men and women over 60 years. J Appl Physiol 20:51.

Levinsky L, Schimert G, et al. (1979) The use of steroids as a potentiator of hypothermic myocardial preservation in man. J Surg Res 26:629.

Levy LA (1980) Hypophosphatemia as a complication of the treatment of hypothermia. Arch Intern Med 140:128.

Liebig J (1852) Animal chemistry. In Liebig's Complete Works on Chemistry. Peterson, Philadelphia.

Linton AC and Ledingham IM (1966) Severe hypothermia with barbiturate intoxication. Lancet 1:24.

Lloyd EL (1973) Accidental hypothermia treated by central rewarming through the airway. Br J Anaesth 45:41.

Lloyd EL and Mitchell B (1974) Factors affecting the onset of ventricular fibrillation in hypothermia. Lancet 2:1294.

McAllister RG, Bourne DW, et al. (1979) Effects of hypothermia on propranolol kinetics. Clin Pharmacol Ther 25:1.

McConn R and DelGuercio LRM (1971) Respiratory function of blood in the acutely ill patients and the effect of steroids. Ann Surg 174:436.

McNicol MW (1967) Respiratory failure and acid-base status in hypothermia. Postgrad Med J 43:674.

Macaron C, Feero S and Goldflies M (1979) Hypothermia in Wernicke's encephalopathy. Postgrad Med 65(2):241.

Maclean D, Taig DR and Emslie-Smith D (1973) Achilles tendon reflex in accidental hypothermia and hypothermic myxoedema. Br Med J 2:87.

Maclean D and Emslie-Smith D (1974) The J loop of the spatial vectorcardiogram in accidental hypothermia in man. Br Heart J 36:621.

Mahajan MD, Myers TJ and Baldini MG (1981) Disseminated intravascular coagulation during rewarming following hypothermia. JAMA 245:2517.

Mangiardi JL, Aiken JE, et al. (1966) Coronary blood flow during moderate and profound hypothermia. J Cardiovasc Res 6:349.

Marcus P (1978) Laboratory comparison of techniques for rewarming hypothermic casualties. Aviat Space Environ Med 49:692.

Marcus P and Redman P (1979) Effect of exercise on thermal comfort during hypothermia. Physiol Behav 22:831.

Morrison JB, Conn ML and Hayward JS (1980) Accidental hypothermia: The effect of initial body temperatures and physique on the rate of rewarming. Aviat Space Environ Med 51:1095.

Mouritzen CV and Andersen MN (1965) Myocardial temperature gradients and ventricular fibrillation during hypothermia. J Thorac Cardiovasc Surg 49:937.

Murphy E and Faul PJ (1963) Accidental hypothermia in the elderly. J Irish Med Assoc 53:4.

Nakayama T, Hammel HT, et al. (1963) Thermal stimulation of electrical activity of single units of the preoptic septal and preoptic neurons in cats. Exp Neurol 19:33.

Naylor GJ and Mettarg A (1977) Profound hypothermia on combined lithium carbonate and diazepam treatment. Br Med J 2:22.

Nesbakken R (1973) Aspects of free fatty acid metabolism during induced hypothermia. Scand J Clin Lab Invest 131:1.

Opie LH (1974) F.F.A., lipolysis, and acute myocardial infarction. Lancet 1:621.

Osborn JJ (1953) Experimental hypothermia: respiratory and blood pH changes in relation to cardiac function. Am J Physiol 175:389.

Ott I (1884) The relation of the nervous system to the temperature of the body. J Nerv Ment Dis 11:141.

Pembry MS (1898) Animal heat. In Textbook of Physiology, Vol 1, EA Schäfer (ed), Pentland, London.

Pickering BG, Bristow GK and Craig DB (1977) Core rewarming by peritoneal irrigration in accidental hypothermia with cardiac arrest. Anesth Analg 56:574.

Pierau FK, Torrey P, and Carpenter DO (1974) Mammalian cold receptor afferents: role of an electrogenic sodium pump in sensory transduction. Brain Res 73:156.

Prakash O, Jonson B, et al. (1978) Cardiorespiratory and metabolic effects of profound hypothermia. Crit Care Med 6:165.

Prec O, Rosenman R, et al. (1949) The cardiovascular effects of acutely-induced hypothermia. J Clin Invest 28:293.

Prescott LF, Peard MC and Wallace IR (1962) Accidental hypothermia, a common condition. Br Med J 2:1367.

Ranson SW and Magoun HW (1939) The hypothalamus. Ergeb Physiol 41:56.

Reuler JB (1978) Hypothermia: Pathophysiology, clinical settings, and management. Ann Intern Med 89:519.

Rittenhouse EA, Mohri H and Merendine KA (1970) Studies of carbohydrate metabolism and serum electrolytes during surface-induced hypothermia with prolonged circulatory arrest. Surgery 69:995.

Rittenhouse EA, Ito DX, et al. (1971) Circulatory dynamics during surface induced hypothermia and after one hour of cardiac arrest. J Thorac Cardiovasc Surg 61:359.

Rosenfeld JB (1963) Acid-base and electrolyte disturbances in hypothermia. Am J Cardiol 12:678.

Rosomoff HL (1964) Pathophysiology of the central nervous system during hypothermia. Acta Neurochirurgica, Supplementum XIII:11.

Ross DN (1956) Principles underlying the application of hypothermia to cardiac surgery. Proc R Soc Med 49:365.

Rudy LW, Boucher JK and Edmunds LH (1972) The effects of deep hypothermia and circulatory arrest on the distribution of systemic blood flow in Rhesus monkeys. J Thorac Cardiovasc Surg 64:706.

Sasaki T (1964) Effect of rapid transposition around the earth on diurnal variation in body temperature. Proc Soc Exp Biol Med 115:1129.

Savides EP and Hoffman BI (1974) Hypothermia, thrombosis, and acute pancreatitis. Br Med J 1:614.

Schissler P, Parker MA and Scott SJ (1981) Profound hypothermia: Value of prolonged cardiopulmonary resuscitation. South Med J 74:474.

Schneider FH and Gillis CN (1966) Hypothermic potentiation of chronotrophic responses of isolated atria to sympathetic nerve stimulation. Am J Physiol 211:890.

Schwab RH, Lewis DW and Killough JH (1964) Electrocardiographic changes occurring in rapidly induced deep hypothermia. Amer J Med Sci 248:290.

Shida H, Morimoto M, et al. (1977) The role of the liver in the changes of acid-base balance and plasma lipids during surface-induced deep hypothermia. Jap J Surg 7:139.

Shida H, Morimoto M, et al. (1981) Inhibitory mechanisms of insulin secretion associated with hypothermic open-heart surgery. Jap J Surg 11:67.

Slotki IN and Oelbaum MH (1980) Recurrent spontaneous hypothermia. Postgrad Med J 56:656.

Southwick FS and Dalglish PH (1980) Recovery after prolonged asystolic cardiac arrest in profound hypothermia. JAMA 243:1250.

Stern S and Braun K (1970) Pulmonary arterial and venous response to cooling: role of alpha adrenergic receptors. Am J Physiol 219:982.

Stoner HB, Frayn KN, et al. (1980) Metabolic aspects of hypothermia in the elderly. Clin Sci 59:19.

Suzuki M, Penn I (1966) The effect of therapeutic agents upon the microcirculation during general hypothermia. Surgery 60:867.

Suzuki J, Kwak R and Okudaira Y (1979) The safe time limit of temporary clamping of cerebral arteries in the direct surgical treatment of intracranial aneurysm under moderate hypothermia. Tohoku J Exp Med 127:1.

Swan H, Virtue RW, et al. (1955) Hypothermia in surgery. Analysis of 100 clinical cases. Ann Surg 142:382.

Tafari N and Gentz J (1974) Aspects of rewarming newborn infants with severe accidental hypothermia. Acta Paediatr Scand 63:595.

Talbott JH (1941) The physiologic and therapeutic effects of hypothermia. N Engl J Med 224:281.

Thauer R (1963) Circulatory adjustments to climatic requirements. in Handbook of Physiology, Vol III. American Physiological Society, Washington, D.C.

Thompson R, Rich J and Chmelik F (1977) Evolutionary changes in the electrocardiogram of severe progressive hypothermia. J Electrocardiol 10:67.

Towne WD, Geiss WP, et al. (1972) Intractable ventricular fibrillation associated with profound accidental hypothermia - successful treatment with partial cardiopulmonary bypass. N Engl J Med 287:1135.

Trevino A, Razi B and Beller BM (1971) The characteristic electrocardiogram of accidental hypothermia. Arch Intern Med 127:470.

Truscott DG, Firor WB, Clein LJ (1973) Accidental profound hypothermia: successful resuscitation by core rewarming and assisted circulation. Arch Surg 106:216.

Vandam LD and Burnap TK (1959) Hypothermia. N Engl J Med 261:546.

Vapaaviori M (1962) Changes in the static elastance and hysteresis of the chest wall and lung in normo - and hypothermia. Acta Physiol Scand 191:65.

Wagner JA, Robinson S and Marino RP (1974) Age and temperature regulation of humans in neutral and cold environments. J Appl Physiol 37:562.

Watts AJ (1972) Hypothermia in the aged: a study of the role of cold sensitivity. Environ Res 5:119.

Westenskow DR, Wong KC and Johnson LL (1979) Physiologic effects of deep hypothermia and microwave rewarming: possible application for neonatal cardiac surgery. Anesth Analg 58:297.

Weyman AE, Greenbaum DM and Grace WJ (1974) Accidental hypothermia in an alcoholic population. Am J Med 56:13.

White JD (1982) Hypothermia: The Bellevue experience. Ann Emerg Med 11:417.

Whittle JL and Bates JH (1979) Thermoregulatory failure secondary to acute illness. Complications and Treatment. Arch Intern Med 139:418.

Wilson O, Hedner P, et al. (1970) Thyroid and adrenal response to acute cold exposure in man. J Appl Physiol 28:53.

Wit A, Wang SC (1967) Effects of increasing ambient temperature on unit activity in the pre-optic-anterior hypothalamus (PO/AH) region. Fed Proc 26:555.

Wit A, Wang SC (1968) Temperature-sensitive neurons in pre-optic/ anterior hypothalamic region: effects of increasing ambient temperature. Am J Physiol 215:1151.

Wood M, Shand DG and Wood AJJ (1980) The sympathetic response to profound hypothermia and circulatory arrest in infants. Can Anaesth Soc J 27:125.

Woolf PD, Hollander CS, et al. (1972) Accidental hypothermia: endocrine function during recovery. J Clin Encrinol Metab 34:460.

Young RSK, Zalneraitis EL and Dooling EC (1980) Neurological outcome in cold water drowning. JAMA 244:1233.