Acclimatization to Cold in Humans

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Hanna Kaciuba-Uscilko, Polish Academy of Sciences, Warsaw, Poland
John E. Greenleaf, Ames Research Center, Moffett Field, California

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Hanna Kaciuba-Uscilko* and John E. Greenleaf

Ames Research Center

SUMMARY

This review focuses on the responses and mechanisms of both natural and artificial acclimatization to a cold environment in mammals, with specific reference to human beings. The purpose is to provide basic information for designers of thermal protection systems for astronauts during intra- and extravehicular activities. Hibernation, heat production, heat loss, vascular responses, body insulation, shivering thermogenesis, water immersion, exercise responses, and clinical symptoms and hypothermia in the elderly are discussed.

INTRODUCTION

Relative to many other mammalian species, man has been provided by nature with rather limited physiological means of defense against cold: poor thermal insulation and minimal ability to produce heat by nonshivering thermogenesis, except in early infancy. On the other hand, being endowed with a highly developed brain and intelligence, man has been able to create a comfortable thermal microclimate (clothing, housing, heating), thereby protecting himself, to a considerable degree, against the deleterious effects of exposure to low temperatures when living permanently or staying temporarily in cold climates. Although the response of man to the stress of cold is essentially behavioral or cultural, there are situations in which he cannot use these abilities of protecting himself against cold, for example, being exposed to cold by accident (e.g., after shipwrecks, a fall from a boat, rapid changes in weather, a temporary soaking through) (Keatinge, 1967; Maclean and Emslie-Smith, 1977; Holmer and Bergh, 1981).

One must also take into consideration that in the life of an individual there are two periods of particular susceptibility to cold: during the few months after birth and in old age. In both these periods of life the thermoregulatory system may be incapable of dealing effectively with changes in environmental conditions that for a normal adult organism would be relatively benign (Maclean and Emslie-Smith, 1977; Robertshaw, 1981).

Physiological response to cold varies with the age and physical fitness of an individual (LeBlanc, 1975; Buskirk, 1978), and depends on the intensity of the cold as well as on the duration of exposure, whether in air or water. Physiological effects of cold are also largely modified in cold-acclimated or cold-acclimatized subjects (LeBlanc, 1975; Carlson and Hsieh, 1974; Folk, 1974; Webster, 1974; Alexander, 1979; Stanier, Mount, and Bligh, 1984).

Physiological adjustment to cold is brought about by two basic mechanisms: (1) reduction of heat loss owing to the increased efficiency of the mechanisms controlling tissue insulation (heat conserving

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* Polish Academy of Sciences Medical Research Centre, Department of Applied Physiology, 00-730, Warsaw, Poland.

mechanisms); and (2) an increase in heat production when thermal conductance cannot be reduced any further and the ambient temperature continues to fall below a "critical" value (curve C in fig. 1).

Heat-conservation mechanisms, usually classified as physical thermoregulatory mechanisms, are the first that are brought into action by cold exposure. They include changes in peripheral blood flow and the countercurrent heat exchange between arterial and venous blood in limbs.

When the heat-conservation mechanisms fail to maintain "normal" body-core temperature, metabolic processes are activated, so that more heat is generated than under thermoneutral conditions in order to compensate for the increased rate of heat loss from the body regulatory heat production.

In adult human subjects the most important mechanism for producing extra heat is shivering in the skeletal muscles; it is initiated by action potentials at the motor nerve end-plate. The term shivering is used to describe various grades of muscle contraction, from an increase in muscle tone through a barely perceptible tremor, to vigorous shivering (Hemingway, 1963).

In newborns (human infants included), as well as in some cold-adapted mammals, the predominant mode of regulatory heat production is nonshivering thermogenesis, occurring mainly in brown adipose tissue (BAT) and mediated by the sympathetic nervous system (Jansky, 1965; Himms-Hagen, 1976; Hassi, 1977; Nicholls and Locke, 1984). Nonshivering heat production is also of special significance in hibernators (Hudson, 1973).

Mammalian species representing hibernators (e.g., the hedgehog, hamster, squirrel, woodchuck) are able to suppress their metabolism and markedly reduce body temperature in a cold environment entering, as a result of those responses, into a state of dormancy or torpidity. This phenomenon is considered by Swan to be an extreme form of energy conservation in vertebrate thermobioenergetics (Swan, 1974). The economized energy use allows the hibernators to survive the cold seasons when food and water are scarce. During arousal from their torpor, the hibernating species rely almost exclusively on nonshivering heat production (Alexander, 1979; Hudson, 1973; Swan, 1974; Foster, 1984).

Unfortunately, not many mammalian species possess such a well-developed ability to suppress metabolism during cold exposure and to become poikilothermic (able to vary body temperature) for a period of time. Maintenance of homeothermia in a cold environment is, energetically speaking, a very expensive process. Since it requires additional energy expenditure and substrate utilization, the capacity for cold thermogenesis may decline significantly during periods of food deprivation or restriction, especially in small infants (Brooke and Cocks, 1973; Folk, 1981) or in very thin individuals, leading, in extreme cases, to hypothermia (Maclean and Emslie-Smith, 1977). This aspect of cold exposure has received little attention.

PHYSIOLOGICAL RESPONSES TO CHRONIC COLD EXPOSURE: ADAPTIVE CHANGES

Definitions

It is generally accepted that prolonged and continuous or continual (intermittent) exposures of a homeotherm to low ambient temperatures result in the development of adaptive changes that favorably affect the response of an individual or those of a whole species to cold stress. The complex changes,

2

including morphological, physiological, biochemical and behavioral characteristics, often make it possible for an organism to survive under conditions of severe cold.

With accumulated knowledge about various means of adjusting to repeated cold exposures, both under laboratory and natural conditions, it became necessary to introduce some working definitions of such terms as cold-acclimatization, cold-acclimation, and habituation, specifying when possible the term cold adaptation.

A definition of acclimatization to cold has been evolving during the past three decades since Hart's (Hart, 1957) introduction of the term in 1957 offered the most convincing and full descriptions of cold acclimatization (see also Folk, 1974, 1981; Budd, 1964; Bligh and Johnson, 1973; Goldsmith, 1967). Folk, considering this phenomenon from the ecological point of view, defined it as "physiological changes occurring in an organism exposed for days or weeks to an extreme environment, which lead to extended tolerance of cold (survival), improved comfort, and decreased energy expenditure (or any of these three)" (Folk, 1974). In Goldsmith's criterion of cold acclimatization an improvement of maintenance of local and vital functions in cold climate is particularly emphasized. In most mammalian species (excluding the hibernators) the enhanced chances of survival in cold environment are possible only when the fall in body temperature, caused by an increased heat loss under these conditions, can be either completely prevented or at least markedly attenuated.

It should be mentioned that the term acclimatization is reserved for the physiological response to a number of environmental factors, including seasonal and climatic (e.g., wind, air-humidity) changes.

When a response to a particular environmental factor, such as ambient temperature, is considered (which is the usual case in laboratory studies) the term acclimation is more appropriate (Bligh and Johnson, 1973).

A gradual quantitative change in the response to cold, namely a diminishing of the physiological response, which results from repeated exposures to low ambient temperature, has been defined as "habituation to cold" (Bligh and Johnson, 1973).

More effective maintenance of homeothermy during prolonged cold exposure can be brought about by two basic mechanisms: (1) increased heat production through the enhancement of metabolic processes (metabolic adaptation) and (2) decreased heat loss by means of increased insulation or its correlates (insulative adaptation). Besides, during prolonged or repeated cold exposures an increased tolerance to lowered heat content in the body may develop, causing a shift of the threshold for shivering to lower temperatures (hypothermic adaptation).

In any classification scheme of biological processes oversimplifications are inevitable. Nevertheless, such a classification is useful in emphasizing some prevailing changes that occur in an organism under conditions of long-term cold exposure in order to reduce the effects of cold stress.

Metabolic Adaptation to Cold

Metabolic adaptation to cold occurs mainly in small, nonhibernating mammals; it is characterized by an enhanced capacity to elevate and sustain heat production during exposure to severe cold. In cold-acclimated, as well as in cold-acclimatized, small mammals, the metabolic rate remains elevated for some time even after the cold stress is removed. The increased tolerance of severe cold is attributed to

development of nonshivering cold-thermogenesis localized mainly (although not exclusively) in brown adipose tissue (BAT) and to the gradual replacement of the less economical shivering thermogenesis (Webster, 1974; Alexander, 1979; Jansky, 1965; Himms-Hagen, 1976). The greater heat production and its altered source site are accompanied by changes in the secretion, release, and physiological effects of catecholamines, with noradrenaline playing a predominant role in the control of nonshivering thermogenesis.

In laboratory rats acclimated to low ambient temperature (5°C) urinary excretion of catecholamines was found to be substantially elevated–up to 6 times normal values–with a peak occurring within the first few days of cold exposure; the thermogenic response to noradrenaline injection was gradually increasing (Leduc, 1961; Depocas, 1960). The increased sensitivity to noradrenaline, attributed mainly to the enlargement of BAT is commonly accepted as an evidence for acclimation to cold in species that possess brown fat.

The physiological significance of some other endocrine changes, repeatedly studied during prolonged cold exposure, is still unclear. The enhanced turnover rate of thyroid hormones found in animals chronically exposed to cold (Heroux and Petrovic, 1969; Ingram and Kaciuba-Uscilko, 1977) seems to be mainly attributable to the cold-induced increase in food intake, whereas the elevated secretion of corticosteroids occurs only when a prolonged exposure to cold is accompanied by restriction of food, leading to a negative energy balance (Boulouard, 1963). Thus, based on these findings, neither the changes in circulating thyroid hormones nor the altered adrenocortical function can be considered as an evidence of cold acclimation.

As first pointed out by Heroux the effects of acclimation and acclimatization of small rodents (e.g., rats, mice) to cold differ in significant respects. First, in the rats acclimated under laboratory conditions, the increased tolerance to cold is nearly exclusively a result of metabolic adaptation, whereas in rats living outdoors, acclimatization to winter conditions, other than the enhanced nonshivering thermogenesis, involved also insulative and vasomotor changes which result in a marked reduction of heat loss. Second, in wild mammals living in areas where winters are severe, an enlargement of BAT precedes winter's cold; it occurs in the fall when food is plentiful. In the laboratory, a period of prolonged cold exposure is necessary to stimulate BAT development (Heroux, 1963).

Hibernation

Small mammals–for example, hamsters, dormice, hedgehogs–living in regions with very severe winters are subjected not only to cold stress during that season, but sometimes also to starvation, and cold injury. Thus, an entry into deep prolonged hibernation seems to be the only means by which such animals can survive. During this state they considerably reduce energy expenditure, and thus energy requirements, which is accompanied by a marked decrease in body temperature. Arousal from dormancy or torpor in hibernators, and their return to a normal, active life is exclusively a result of nonshivering thermogenesis, accompanied by a very high sympathetic activity (Hudson, 1973). It is important in this respect that brown fat from hibernators does not involute during their development and that the BAT mitochondria never appear to lose the 32,000-Mr protein (Nicholls and Locke, 1984).

Insulative Adaptation to Cold

It is commonly known that larger mammals develop thicker hair coats in winter, which allow them to decrease heat elimination from the body, even at extremely low ambient temperatures. It should be emphasized, however, that the rate of hair coat, or wool growth is mainly related to the length of daylight, since the most rapid growth of these insulative covers occurs in autumn. So the animals become, in a way, pre-adjusted to the forthcoming winter. Cold stress per se does not affect wool growth in sheep (Slonim, 1974) or pelage growth in cattle (Morris, 1961), although in the latter it does reduce shedding. Pigs raised in cold environments become unusually hairy, but it is not known whether it is caused by increased growth of hair coat, reduced shedding of pelage, or both (Stanier, Mount, and Bligh, 1984; Webster, 1970).

Greatly increased body insulation in the form of fur (e.g., in a polar fox or wolf) or subcutaneous fat (e.g., in a seal) observed commonly in arctic animals has been described by Jansky as "inherited mechanisms" of insulative cold adaptation (Jansky, 1965). The efficiency of heat-loss reduction in the mentioned species is such that even in severe cold they do not need to increase heat production, and can survive arctic winters in spite of the scant winter food supply.

An increase in the thickness of subcutaneous fat would also be an indicator of cold acclimatization in domestic animals and man, considering the insulative properties of the tissue. However, in spite of the increased food intake in animals kept in the cold, they have apparently less fat and more muscle than those kept in the hot environment, thus indicating an increase in the ratio of the "active tissue mass" to the total weight (Mount, 1968).

Hypothermic Cold Adaptation

In the last few decades, hypothermic cold adaptation has been demonstrated to be a much more common and important phenomenon than was previously thought (Webster, 1974; Macari, Dauncey, and Ingram, 1983). In this type of adaptation, precision of thermoregulation is diminished and as a result hypothermia may develop, the reason being that the threshold for cold defense reactions is shifted to the lower levels of skin and to the cervical spinal cord temperatures (fig. 2). Thus, the stimulus necessary to induce shivering must be greater in cold-acclimated animals than in control animals (Brück, 1976; Brück et al., 1970). Reducing shivering leads to (1) more economical, although less precise temperature regulation, and (2) increased cold-tolerance.

These effects can be achieved either by prolonged or intermittent whole-body cold exposures both in laboratory animals and in man (Macari, Dauncey, and Ingram, 1983). Both these procedures result in a reduced metabolic response to cold (shivering) and a decrease in core body temperature. Besides, the magnitude of discomfort caused by exposure to low ambient temperatures is markedly diminished (Macari, Dauncey, and Ingram, 1983). The reduced thermogenic response to cold (hypothermic adaptation) may be also attributed to habituation of an individual to repeated cold stimuli. Australian aborigines and the Korean women pearl divers (called amas) are good examples of this type of cold adaptation (see section entitled "Acclimatization to Cold in Man").

PHYSIOLOGICAL EFFECTS OF ACUTE COLD EXPOSURE

Changes in Heat Loss from Body

Core temperature, that is, the temperature of brain as well as of the thoracic and abdominal viscera of homeothermic organisms, is normally maintained at a higher level than that of the ambient air or water. However, since heat is lost to the environment from the surface of the body, the skin is usually cooler than the core. The temperature gradient between the body core and skin surface can be modified markedly by alterations in the insulation of the skin and superficial tissues, which helps to regulate heat loss by convection and conduction. Tissue insulation is determined by morphological factors such as the thickness of the skin and subcutaneous fat, and by the rate of blood flow through the superficial tissues, especially in the extremities.

Cold-induced vasoconstriction– When the human body is exposed to cold, cutaneous blood flow can be promptly reduced by an intense constriction of the skin resistance vessels, the arteriovenous anastomoses, and the veins in the skin. By this mechanism, heat transfer from the body core to the body surface is attenuated, skin temperature decreases, and less heat is lost to the environment.

The skin vessels of the human hand constrict so effectively that the ratio of maximum-to-minimum blood flow can be 60 to 1, whereas the same ratio in the body shell is about 6 to 1 (Thompson, 1977). Blood flow through the hand is minimal (less than 1 ml/min) at an ambient temperature of about 10°C; below this temperature periodic vasodilation occurs (Burton and Edholm, 1955).

Cutaneous vasoconstriction also decreases heat loss from the body by directing venous blood flow through the deep veins that are close to the arteries. In this way arterial blood, entering the limb at a relatively high temperature, comes into close contact with cooled venous blood. A countercurrent heat exchange is established so that heat is conducted directly across the vessel walls from arterial to venous blood. Because of this anatomical arrangement, metabolic heat is conserved within the body core at the expense of further cooling of the extremities.

Patients with Raynaud's disease (Shepherd and Vanhoutte, 1979) or those with anorexia nervosa (Luck and Wakeling, 1981) are particularly sensitive and show an increased vasoreactivity to cold stimuli that is attributed to a local defect in the vessels, but the exact mechanism underlying the syndrome is unknown.

The efferent sympathetic nerves produce vasoconstriction. They descend from the posterior hypothalamus to the spinal cord, leaving the spinal cord through the ventral roots to the sympathetic chain where each preganglionic neuron synapses with a number of postganglionic neurons; acetylcholine is the transmitter. The postganglionic fibers join with cutaneous nerve bundles and innervate blood vessels in the skin; noradrenaline is the transmitter. The vasoconstrictor receptors in the smooth muscle of the skin arteries and veins, as well as in the arteriovenous anastomoses, are alpha-adrenergic receptors (Folk, 1981).

The response of cutaneous blood vessels to their sympathetic stimulation can be reinforced by local cooling of skin.

Cold-induced vasodilation– When cold is severe enough and skin temperature falls below 10°C, cutaneous blood vessels in the areas with arterio-venous anastomoses (e.g., in the hands and feet) dilate

periodically. Waves of vasodilation are particularly well pronounced when the body core is warm and only the peripheral parts are exposed to cold. Under these conditions the brief episodes of vasodilation in the skin of the extremities help to maintain the normal function of the extremities and to prevent severe damage to their tissues when they approach the freezing point (Shepherd and Vanhoutte, 1979).

The pattern of cold-induced vasodilation (CIVD) in man was first described in 1930 by Lewis who called it the hunting phenomenon (Lewis, 1930). The author demonstrated that when a finger is immersed in ice water the skin temperature falls steeply to 1°C-1.5°C. After a few minutes, however, it rises rapidly 7°C-10°C, and then decreases again to nearly 0°C (fig. 2).

The cycle is repeated several times during the local cold exposure. The alterations in the skin temperature are due to cyclic fluctuations of cutaneous blood flow.

The sudden increase in the cutaneous temperature (hunting reaction) depends, to a marked degree, on a general thermal state of the body–the warmer the body core the greater the local increases in skin temperature during CIVD. Also, the intensity of the "hunting rhythm" is variable in normal subjects. Maintenance of this phenomenon was demonstrated in sympathectomized patients, and it persisted in a modified form even after degeneration of all sensory and motor nerves (Webster, 1974).

The hunting phenomenon is most probably not the sole factor contributing to CIVD in man, since cold vasodilation occurs often without any obvious signs of temperature fluctuations (Burton and Edholm, 1955).

When compared with other mammalian species, man's capacity for CIVD is limited, and as a result frostbite or prolonged ischemia in the extremities have been frequently reported when unacclimatized men were exposed to severe cold. In people used to working in cold surroundings, CIVD is more pronounced.

The exact nature of the vasodilator stimuli acting during cold exposure is still uncertain, although several mechanisms of CIVD have been considered, including the effects of a cold-induced "paralysis" of the vascular smooth muscle and an action of locally released vasodilator substances (e.g., bradykinin) or metabolites, the former being the most convincing (Keatinge, 1967; Maclean and Emslie-Smith, 1977; Webster, 1974). In 1958, Keatinge demonstrated on an animal model that the responses of isolated arteries to noradrenaline are blocked at low temperatures, indicating that cold most probably inhibits the normal effect of the neurohormone on the cell membrane (Keatinge, 1958). The "paralysis" of the vascular muscle could be reversed by delivery of warm blood, restoring the normal sympathetic vasoconstriction.

As one can see, the vasomotor responses to cold described previously are designed to serve two seemingly conflicting needs: to minimize heat loss from the body by cold-induced vasoconstriction, and to maintain the integrity of the tissues exposed to cold, especially in the extremities, at the expense of additional whole body heat loss by CIVD.

Heat loss from the head and trunk– At low ambient temperatures (<4°C) heat loss from the head may account for half of the total resting heat production in man (Keatinge, 1967). Human facial circulation does not undergo the cold reflex vasoconstriction (Steegmann, 1979), but it is assumed that the facial skin cools passively by a direct local action of cold. However, because of its proximity to the thermal core areas, facial temperature stabilizes well above freezing, even under conditions of severe cold; this explains the relatively rare incidences of the facial frostbite.

Much of the heat from the human trunk is transferred from deep tissues and organs to the body surface by simple physical conductance, which is not under physiological control. Thus, a man immersed in relatively cold water (22°C), loses very little heat from the hands and feet, a result of the greatly reduced tissue conductance in the extremities; much more heat is lost from the trunk because of high tissue conductance to this body area.

Subcutaneous fat as protection against excessive heat loss– The subcutaneous fat layer provides the extra insulation that substantially reduces heat loss from the body, extends body core cooling, and hence extends the thermal drive for metabolic responses to cold. The minimum core temperature (rectal temperature, T_{re}) during exposure to 10°C or 15°C air in subjects wearing only shorts has been found to be directly related to the percent of body fat:

$$T_{re}(min)(°C) = 36.33 + 0.011\% \text{ fat (at 10°C)}$$

This indicates that the body core cools less in obese individuals than in lean ones (Buskirk, Thompson, and Whedon, 1963).

Moreover, an inverse relationship was demonstrated between the surface temperature, represented by the mean weighted skin temperature (MWST) and the percent body fat: MWST (8 points) (°C) = 26.99 - 0.58% fat, which means that the core temperatures of obese subjects are higher and their body-surface temperatures are lower than those of lean subjects when both are exposed to cold for periods of an hour or more.

Experiments performed both in cold water and in air indicate a close relationship between the total body fat and the metabolic responses to cold in man (Buskirk, 1978). Exposure to 10°C air for a couple of hours is necessary to produce the metabolic response to cold (shivering) in obese subjects, whereas in lean subjects this response is noted after only 30 min. The influence of body fat on preventing or delaying the metabolic response to cold results mainly from its role in peripheral insulation.

However, a possible "active" role of body fat in the metabolic reaction to cold cannot be excluded, particularly since lowering of the respiratory quotient (R) with duration of cold exposure has been seen to be more pronounced in obese than in lean people. This suggests a greater contribution of lipids to the metabolic processes in obese people (Buskirk, Thompson, and Whedon, 1963).

Enhanced Heat Production in Response to Cold in Man

Increase in muscle tone and involuntary muscle contractions: shivering– Involuntary contractions of the skeletal muscle groups throughout the body–an important source of the regulatory heat production–can be initiated rapidly and continued for a long period of cold exposure. Since very little external work is performed during shivering, almost all the energy released appears promptly as heat.

An increase in muscle tone, termed the "preshivering" or "thermal" muscle tone, is the primary muscle response to cold exposure. This initial stage of shivering is characterized by the frequency (10-12/sec) and magnitude (0.5-3.0 µV) of the microtremor. Both the preshivering tone and periodic bursts of synchronized activity may be detected electromyographically by recording action potentials of muscle groups (e.g., with electrodes fastened to the skin overlying the muscle) (Hemingway, 1963). Under conditions of longer or more severe exposure to cold, separate peaks of electrical potentials cumulate into typical bursts repeating themselves regularly in a characteristic phasic manner (Stuart et al., 1963). Their

magnitude increases with the intensity of the cold stimulus. Electromyographic examination of the shivering muscle reveals that the rhythmic bursts of potentials during the contraction phase of each shivering cycle are followed by a drop of electrical activity to a resting state in the relaxation phase.

Both preshivering tone and shivering contractions first appear in extensor muscles and proximal muscles on the upper limbs or trunk, and then in the extremities. Almost all skeletal muscles, except those lacking stretch receptors (e.g., middle ear, face, and perineum), are capable of producing heat by shivering. It is interesting that the frequency of shivering is nearly identical in all the muscles of an organism and, according to results from most studies, it changes little despite rhythmic alterations in amplitude.

Using the hind limb of the young ox, Bell, Thompson, and Findley (1974) convincingly demonstrated that cold sufficient to double the total metabolic rate of the animal resulted in an approximately tenfold increase in the mean leg oxygen uptake. The enhanced contribution of the shivering hind leg to the metabolic response to cold coincided with marked elevations (up to sixfold) in blood flow through the musculature of this area, and increases (up to fourfold) of arteriovenous oxygen saturation.

Magnitude of shivering thermogenesis– The "maximal shivering capacity" is difficult to evaluate precisely. Studies of maximal shivering have too often been carried out at temperatures too high to cause the maximal shivering response, or they allowed insufficient time for the response to develop. Besides, in many mammalian species a part of the total heat produced in response to cold exposure may originate from nonshivering thermogenesis, and quantitative differentiation between these two means of heat production (shivering and nonshivering) is rather difficult. Based on data reported by various authors it appears that animal species differ considerably in their maximal capacity of shivering (fig. 3).

In small mammals the heat produced by shivering seldom exceeds 3 times their resting metabolic rate, whereas, in the large mammals, including man, the average increase in metabolism is often 4 to 5.5 times the level of the basal metabolic rate (BMR) (Alexander, 1979; Hemingway, 1963; Jansky, 1965; Iampietro et al., 1960). The highest limit of shivering thermogenesis has been reported (Chatonnet and Minaire, 1966) for the dog (10 times basal) and sheep (Bennett, 1972) (8 to 10 times basal).

In human subjects exposed to severe cold (-29°C) for 4 hr, both the integrated electrical activity of muscle and heat production increased gradually with time of cold exposure: the latter averaged 243 $kJ \cdot m^2 \cdot hr^{-1}$ in the first hour and was 402 $kJ \cdot m^2 \cdot hr^{-1}$ during the fourth hour (Glickman et al., 1967).

The onset and intensity of shivering at a given ambient temperature, as well as the critical mean skin temperature for this metabolic response in men exposed to cold, depend on several factors, for example, physical fitness, body size and insulation, and the level of habitual physical activity (Buskirk, 1978; Iampietro, Vaughan et al., 1960; Brück, Baum and Schwennicke, 1976). Shivering tends to be suppressed by voluntary muscle contractions (physical exercise), although this inhibition does not occur when deep-body temperature is reduced (Burton and Edholm, 1955; Nadel, Holmer et al., 1974). In terms of maintaining body heat, the efficiency of shivering is rather low, averaging 10% in men exposed to 10°C and 11.5% in those exposed to -3° (Horvath et al., 1956; Spurr, Hutt, and Horvath, 1957). The relatively low efficiency of shivering is attributed mainly to the greatly elevated convective loss of heat, which increases heat transfer from the body to the environment. In animals covered with pelage, for example, goats or oxen, shivering may appear to be 100% efficient (Alexander, 1979).

Control of shivering– Shivering is controlled by the brain neurons that are activated by stimulation of the cutaneous cold receptors, and is inhibited by central warm receptors (Hensel, 1974; Benzinger, 1969).

Electrical stimulation of different points in the brain of experimental animals, as well as lesion experiments, provided evidence that the primary "center" involved in the control of shivering is located in the dorsomedial posterior hypothalamus, near the wall of the third ventricle (Hemingway, 1963). Electrical stimulation of this center initiates involuntary muscle contractions, whereas its destruction (e.g., by a lesion) abolishes the shivering response to cold. Thus, this center must be intact and have neural connections with lower motor centers for shivering to occur. Besides the primary center, a few secondary centers, involved mainly in the suppression of shivering, were demonstrated in the brain. There are at least four suppression regions for shivering: (1) in the ventro-lateral posterior hypothalamus, (2) in the ventro-medial forebrain septum, (3) in the ventro-medial preoptic region of the anterior hypothalamus, and (4) at some points of the cerebral cortex.

Removal of the secondary centers does not prevent the spontaneous shivering caused by cold or shivering induced by stimulation of the primary hypothalamic center.

The wide distribution in the brain of the sites at which stimulation causes suppression of shivering (secondary centers) seems to have, at least teleological, justification. The skeletal muscles used for shivering are also used for emergency purposes of flight and defense. The latter would take priority in the survival of an animal or man in life-threatening situations. A mechanism causing the rapid cessation of shivering and allowing the muscles to be used for more urgent defense reactions is of importance for life preservation.

Injections of various neurotransmitters into the hypothalamus of conscious experimental animals revealed that noradrenaline is most likely the main neurotransmitter that stimulates shivering. Moreover, cold exposure was found to increase noradrenaline turnover in the hypothalamus (Thompson, 1977).

Efferent pathways from the hypothalamus travel through the midbrain, the reticular formation in the pons and medulla, and down the spinal cord. In the spinal cord they synapse with motoneurons, which innervate the skeletal muscles.

Although shivering is controlled by the brain neurons the characteristic rhythm of shivering is generated at the spinal level. It should be also mentioned that shivering can be evoked by cooling the spinal cord. Besides, the shivering induced by external or central cold stimulation, as well as by general hypothermia, is enhanced by spinal cord cooling and it is reduced or even abolished by spinal cord warming (Simon, 1974).

Energy sources for shivering thermogenesis– Similarly to the voluntary muscle contractions, the immediate energy source for shivering derives from hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate. The rapid formation of ADP during shivering accelerates substrate oxidation in mitochondria, which is accompanied by a loss of energy as heat. Although carbohydrates are the important fuel for contracting muscle there is no longer any doubt that oxidation of fat plays a vital role in providing energy for sustained shivering (Alexander, 1979).

During the initial stages of cold exposure, energy substrates for shivering are drawn mainly from endogenous (intramuscular) stores of carbohydrates, in the form of glycogen, and of fat in the form of triglycerides. These stores are rather limited, when expressed as a percentage of tissue mass. However, since skeletal muscles are such a large proportion of the total body mass, the muscle endogenous stores can cover energy demands of shivering for quite a long time of cold exposure. Besides, during cold stress, blood glucose and plasma free fatty acid (FFA) concentrations increase significantly (Alexander, 1979; Thompson, 1977). The quantitative significance of these extramuscular energy substrates for

shivering thermogenesis has not been fully evaluated. It seems likely, however, that the severity and duration of cold stress, the nutritional state of an organism, the preceding level of physical activity, the hormonal status, and the degree of acclimatization to cold can modify utilization of these substrates by shivering muscles. Results from experiments performed on animals provided evidence that hepatic glucose production, as well as glucose uptake and oxidation by skeletal muscles, increases during shivering (Thompson, 1977; Smith and Davidson, 1982; Minaire et al., 1982). The changes in hepatic glucose production have been commonly attributed to the synergistic stimulatory effects of glucagon, adrenaline, and cortisol on glycogenolysis and gluconeogenesis (Alexander, 1979). Increased concentrations of these hormones in blood on response to cold stress were found both in animals and men (Thompson, 1977; Seitz et al., 1981). However, recently an immediate contribution of the hormones to the control of glucose kinetics during shivering has been questioned, since glucose production during acute cold exposure was found to be unaffected by adrenodemedullation and no changes in glucagon level were detected for the first hour in the cold (Minaire, Forchion, and Fréminet, 1982).

Shivering stimulates glucose uptake by skeletal muscles in spite of the inhibition of insulin secretion upon cold exposure (Smith and Davidson, 1982; Forchion et al., 1977; Sasaki and Takahashi, 1980). However, a small quantity of insulin has to be present to prevent excessive mobilization of lipids, which, in turn, inhibit carbohydrate utilization.

Fasted animals fail to increase glucose turnover rate and muscle glucose uptake when exposed to cold, most likely because of the enhanced supply of fatty acids and ketone bodies to the contracting muscles (Alexander, 1979). The enhanced lipolysis with concomitant release of free fatty acids and glycerol from adipose tissue to blood results from the cold-induced activation of the sympatho-adrenal system and reduced insulin secretion. Only a part of the FFAs produced by lipolysis is promptly utilized by shivering muscles (Thompson, 1977); most of them are re-esterified in the liver and then released into circulation in the form of very low density lipoprotein, which can be also used by contracting muscles after previous hydrolysis.

The presence of thyroid hormones (thyroxine and triiodothyronine) is necessary to maintain lipolysis and thermogenesis on a high level during cold exposure. Although neither blood concentration of these hormones nor their turnover is affected by cold, they play a permissive role in the metabolic responses to other catabolic hormones, for example, catecholamines under conditions of acute cold-exposure (Alexander, 1979; Weeke and Gundersen, 1983).

PHYSIOLOGICAL RESPONSES TO COLD IN HUMAN INFANTS

At the moment of birth an infant is exposed to a severe cold stress, since from the warm and insulated maternal environment it is delivered wet and naked to the extrauterus environment, where the temperature is often 15°C lower than that of the womb.

Even in small premature babies the homeothermic pattern of temperature regulation exists at the time of birth (Brück, 1961). Newborn infants respond to the cold environment first by cutaneous vasoconstriction, and then by an increase in nonshivering heat production evoked, in a reflex way, by changes in skin (mainly facial) temperature. However, in comparison with adults they are handicapped by a relatively high body surface to mass index, their thin skin, a scanty subcutaneous fat layer, their inability to shiver, and their very poor motor development. These are the factors that account for the thermal instability of newborn babies (Robertshaw, 1981; Hey, 1969; Fenner and List, 1971; Rylander, 1972).

Metabolic Changes after Birth

The lower critical temperature, below which the rate of metabolic heat production increases to maintain thermal balance, is of the order of 34°C-36°C immediately after birth (Hey, 1969), and tends to be lower with increasing body weight (fig. 4).

The resting metabolic rate of infants, measured in the period between 0.5 and 3.5 hr after feeding at an ambient temperature close to 35°C, is approximately 5.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ within the first 12 hr following birth, 8 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ from day 2 to day 20 of life, and 9.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ at 2 months of age (Hey, 1969).

The low metabolic rate at birth is close to that of the fetus near-term and that of the maternal organism. The postnatal rise in the metabolic rate is particularly marked in babies that are small for their age, but it is delayed by 3-7 days in the low-birth-weight infants.

The reason for the fairly rapid increase in metabolism within the first few days of life has not been explained, although it can be speculated that an increase in the mass of metabolically active tissues in relation to body weight, following a reduction in the extracellular body fluid volume, may be a factor (Robertshaw, 1981).

During the first days of life an infant produces heat by metabolizing his carbohydrate and fat stores. Within a few hours following birth, the infant's liver glycogen is nearly completely exhausted and blood glucose concentration frequently falls to 1.11-1.67 mmol·liter^{-1}, which in adults would be regarded as severe hypoglycemia. Mobilization and utilization of fat stores (mainly of brown adipose tissue origin) continues for much longer, and there are suggestions that in the early postnatal period glycerol could supplement carbohydrates as an energy substrate for the brain (Heim, 1971).

Metabolic Responses in Newborn Babies

The naked baby is remarkably sensitive to even a small decrease in environmental temperature (Hey, 1969; Rylander, 1972). However, the metabolic response to cold is only slight during the first 12 hr after birth (0.56 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ for each 1°C fall of ambient temperature below 33°C) in comparison with that found in infants more than 4 days old (1.25 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ for each 1°C).

The maximum metabolic response to cold stress (the summit metabolism) measured in infants between 3 and 11 days of age at an ambient temperature of 26°C amounts to 16.8 ±(SD) 0.9 ml·kg^{-1}·min^{-1}, exceeding the resting metabolic rate by approximately 2.5 times. No further increase in heat production occurs when ambient temperature is lowered to 22°C-24°C for 10 min (Hey, 1969). At low ambient temperature all babies become very active, but in spite of the increased activity their rectal temperatures start to fall at a rate of more than 1°C/hr, which indicates that even a vigorous healthy baby left unclothed in a room at a low temperature may eventually become hypothermic. Besides, even in properly clothed babies, cooling of uncovered faces or the breathing of cool air may increase heat production by 25%-60% (Heim, 1971).

Brown Adipose Tissue

Similarly to newborns of many other mammalian species, human infants increase their rate of heat production in response to cold by neural stimulation of BAT, although some authors claim that other tissues, for example, muscles and particularly the brain, which is responsible for about 70% of the resting heat production in newborns, may play a predominant role in the metabolic response to cold during the first days of postnatal life.

BAT in infants is situated between the shoulder blades, along the spine, behind the breastbone and around the neck. It can be also found perirenally, as well as around cervical blood vessels.

BAT is detected in fetuses older than 19 weeks, and it is seldom present in adults above 24 years of age (Hassi, 1977). The average amount of BAT in the human neonates is about 15 g, but it may amount to 30-40 g (Heim, 1971). In case of complete oxidation of lipids present in this tissue (about 9 g), approximately 358.7 kJ of heat can be generated, thus meeting the 24-hr energy demands of a newborn baby weighing 3,000 g, and exposed to 25°-26°C.

Morphology of BAT

BAT is composed of compact fat lobes that contain mostly brown adipose cells. The tissue is supplied with rich sympathetic innervation, and frequent gap junctions between adipocytes (fig. 5), which most probably distribute the nerve stimulus throughout the tissue (Schneider-Picard, Carpentier, and Orci, 1980). The color of BAT is caused by the presence of an iron-containing cytochrome; it becomes particularly apparent after fat depletion from the tissue. In comparison with white adipocytes, brown adipose cells have more cytoplasm, a centrally located nucleus, and are richly filled with large mitochondria packed with cristae (fig. 5). Another characteristic of these cells is the scattering of numerous, variously sized lipid inclusions in the cytoplasm.

Mechanisms of Thermogenesis in BAT

The morphological structure of BAT, which distinguishes it from white fat, fulfills the specialized heat-producing function of this tissue. According to the recently presented evidence, BAT possesses the unique ability of generating heat by "uncoupling" or "loose coupling" of oxydation with ATP synthesis, so heat is produced instead of ATP (Nicholls and Locke, 1984; Himms-Hagen, 1984; Bukowiecki, 1984). This ability is apparently related to the brown-fat-specific protein with a molecular weight of 32,000, which is found in the inner mitochondrial membrane (Smith and Brück, 1981, in fig. 6)

The amount of heat produced in BAT is precisely controlled by the central nervous system. According to Horowitz et al. (Horowitz, Fuller, and Horowitz, 1976), the overall control of BAT (Doi et al., 1979 in fig. 7) involves (1) neural signals from the central nervous system (CNS) over sympathetic nerves, (2) production of heat by the tissue, (3) monitoring of blood temperature from BAT by thermal receptors, and (4) encoding of the temperature as neural signals traveling back to the CNS.

Noradrenaline (NA) released by the sympathetic nerve endings interacts with beta-adrenergic receptors of the brown adipocyte membrane, altering the membrane properties and initiating a chain of events that finally lead to enhanced heat production in the tissue.

An increased cell membrane permeability causes stimulation of NA^+/K^+ pump activity, which may also enhance, at least to some degree, the rate at which chemical energy in the form of ATP is converted into heat. Besides, because of the increased permeability, Na^+ can more easily enter the cell, and as the ions move down the electrochemical gradient their potential energy is also converted into heat (Giardier and Seydoux, 1971). Noradrenaline-induced stimulation of the membrane-bound enzyme, adenylate cyclase, and subsequently of cyclic adenosine monophosphate leads to the activation of protein kinase and then of the hormone-sensitive lipase, resulting in hydrolysis of the intracellular triglycerides. Fatty acids released in this process serve as the main substrate for the mitochondrial oxidation.

However, to enter mitochondria the fatty acids must be first activated to acyl-CoA by one of two pathways: (1) the major carnitine-dependent, or (2) slow carnitine-independent. In the former, free fatty acids are activated by thiokinase (in the presence of ATP) to fatty acyl-CoA esters, react with carnitine to form fatty acyl carnitine, and in this form pass through the mitochondrial membrane. Re-conversion of fatty acyl-CoA esters occurs within the mitochondria. In the slower carnitine-independent pathway, free fatty acids enter the mitochondria unchanged, where they are activated by thiokinase within the mitochondria.

The activated fatty acids are then degraded by beta-oxidation (a process requiring ATP) to acetyl-CoA, which enters the tricarboxylic acid cycle to yield CO_2, ATP, or GTP, and energy-rich protons in the form of NADH. The energy-rich protons finally enter the electron transport chain in the inner mitochondrial membrane.

In the mitochondria of several tissues (e.g., muscle, liver) the final products are water and energy, mainly in the form of ATP, plus heat. Brown fat mitochondria possess a well-developed electron transport chain. However, in comparison with other tissues, the chain appears to be less tightly coupled to the production of ATP from ADP. In BAT fatty acids seem to play the dual role of a substrate and an uncoupling messenger, since the electron transport chain in this tissue has been shown to be uncoupled by high concentrations of free fatty acids. The inner mitochondrial membrane contains a specific protein–32,000 M_r with a proton conductance pathway that allows protons to leave the electron transport chain, pass through the membrane, and dissipate their energy as heat.

It has been recently suggested that free fatty acids may interact with the 32,000-M_r protein, inducing a conductance change in the membrane (Nicholls and Locke, 1984). Although there is no direct evidence to support the concept, it has been proved that the high sensitivity to fatty acid uncoupling depends on the presence of the 32,000-M_r protein and that even low concentrations of fatty acids influence the nucleotide-binding (to MgATP) properties of the protein. Nicholls and Locke postulate the following sequence of events in brown adipose tissue leading to the enhanced thermogenesis. (1) Noradrenaline binds to the beta-receptor, (2) cyclic AMP levels in the cytosol rise, (3) protein kinase is activated, (4) lipase is phosphorylated and activated, (5) fatty acids are liberated and activated to acylcarnitine, (6) oxidation of acylcarnitine is inhibited by the respiratory control, and the acylcarnitine as well as acyl-CoA pools fill up, (7) free fatty acids begin to accumulate, reversing the nucleotide inhibition of the 32,000-M_r protein, and (8) the increased proton conductance allows acylcarnitine to be oxidized and a steady-state concentration of fatty acids is reached with a balance between lipolysis and oxidation. On termination of lipolysis all the events would occur in reverse (Nicholls and Locke, 1984).

Factors Affecting the Amount of BAT in Newborns

As was demonstrated on an animal model, the amount of BAT in neonates can be increased by changes in diet or by cold exposure of their mothers during pregnancy. Thus, short periods of starvation toward the end of the gestation period, or feeding with a diet containing linoleic acid increases the lipid content of the tissue in newborns and enhances the thermogenic capacity of BAT. On the contrary, prolonged maternal undernutrition or retardation of fetal growth reduce the proportion of brown fat in the neonates, leading to a decreased tolerance of cold in newborns (Alexander, 1979).

ACCLIMATIZATION TO COLD IN MAN

Because the evidence for acclimatization to cold in man is much less compelling than that for acclimatization in animals there are some who question whether it exists at all (Goldsmith, 1967).

Man is seldom subjected to prolonged whole-body cold exposure, even when living and working in a cold climate. When a civilized man moves to polar regions he usually takes his warm microclimate with him, thus protecting himself against the discomforts brought about by the severe weather. Thus residence in cold regions leads at most to intermittent exposures to cold, usually associated with outdoor work or sports activities.

Natives of polar regions, for example, Eskimos or Lapps, have developed highly efficient means of sheltering and clothing that protect them against an excessive heat loss even at extremely low ambient temperatures. It is, therefore, not surprising that it is difficult to find circumstances under which acclimatization to cold in man could develop and be clearly demonstrated.

On the other hand, the findings ascribed to acclimation or acclimatization in animals cannot serve as direct reference data for man because of species differences. When a laboratory animal (e.g., rat, guinea pig) is acclimated to cold for a few weeks, this period covers a much greater part of its life span than it does for human subjects exposed to cold for the same length of time (Zeisberger and Brück, 1976).

Metabolic Adaptation in Man

An intensive search for evidence of metabolic adaptation to cold in man has yielded conflicting and in most cases unexpected results. Wilson, reporting on his 2-year field studies carried out on a selected group of Norwegian, British, and Swedish men wintering in the Antarctic, found no influence of the sojourn on the mean level of BMR (Zeisberger and Brück, 1976). On the other hand, his results indicate a seasonal trend toward lower BMR during the more sedentary winter period and higher values during the active spring and autumn seasons. A decreased rate of heat production in winter, spent in polar regions, has also been reported by other investigators (Wilson, 1966; LeBlanc, 1956).

An opposite trend of the seasonal BMR changes with an increase in winter (by approximately 10%) and a decrease in summer has been convincingly and repeatedly demonstrated in Japanese populations (Milan, Elsner, and Rodahl, 1961; Yoshimura et al., 1966). This rhythmicity is assumed to be a physiological response to cold stimuli. The lack of this response in Western people, even those living temporarily in Japan in Japanese style houses that are not equipped with modern heating systems, has been

ascribed to differences in body surface area, diet, and physical activity throughout the year, with the surface area differences thought to be the most important.

A highly significant negative correlation between body surface and the magnitude of seasonal variation in basal metabolism confirms a possibility of the more pronounced seasonal variation in small individuals than in larger, heavily built subjects (Milan, Elsner, and Rodahl, 1961).

A consistent, reversible increase in BMR (by approximately 30%) in winter occurs also in Korean women pearl divers (called amas) who dive throughout the year (Doi et al., 1979). Such a considerable enhancement of BMR in winter, when the seawater temperature is at its lowest (~10°C), is primarily a result of cold exposure.

The Korean amas are subjected to daily, whole-body cold stress greater than any other group of human subjects studied (0°C air, 10°C water in winter). It should be emphasized that amas dive throughout the year wearing only cotton bathing suits. They start diving at 12 years of age and continue until they are past 50. Because they are exposed repeatedly to severe cold over a long period, amas make a convincing example of acclimatization to cold, including the metabolic component of this process (Doi et al., 1979).

The practical value of the increased BMR seems of minor importance as a defense mechanism against body cooling in winter. Moreover, it is an energetically wasteful process. Nevertheless, the enhancement of BMR, which is not attributed to dietary changes, indicates that man is capable of metabolic adaptation when subjected to repeated or prolonged and severe body cooling. Although an exact mechanism of the metabolic alterations remains to be identified, it seems that stimulation of the sympathetic activity, as judged by a considerable rise in the urinary NA excretion, and an enhanced participation of catecholamines in the control of thermogenesis (nonshivering ?) play a role in that mechanism. Any importance of thyroid hormones is doubtful, although an increased utilization of these hormones by peripheral tissues has been suggested (Doi et al., 1979).

To find out whether prolonged exposures to low ambient temperatures modify the metabolic response to the acute cold-stress body temperatures, the metabolic rate and magnitude of shivering were measured in men both under laboratory conditions and during polar expeditions (Zeisberger and Brück, 1976; Wilson, 1966; Yoshimura et al., 1966; Hong, 1973; Budd and Warhaft, 1966). The most common finding, a marked decline in the shivering response to cold-stress in acclimated human subjects, has been attributed by some authors (Yoshimura et al., 1966; Davis, 1963) to nonshivering thermogenesis mediated, according to Doi and his co-workers (Doi et al., 1979), by an enhanced mobilization and utilization of FFA, owing to activation of the sympathetic nervous system (fig. 8). An inhibition of FFA mobilization from adipose tissue by nicotinic acid, administered before cold exposure, resulted in less elevated heat production, a significant fall of plasma FFA and ketone body (beta hydroxybutyrate) concentrations, and a considerable enhancement of shivering. A significant positive correlation between the plasma FFA level and heat production, as well as an inverse relationship between the respiratory exchange ratio (R_E) and the plasma FFA concentration, support the suggestion that the increase in heat production during cold exposure of men acclimatized to cold is associated with increased FFA mobilization and utilization.

Replacement of shivering by nonshivering thermogenesis has been suggested as an explanation of these findings; however, the possibility that the elevated heat production without visible shivering is due to increased sustained muscular tension with possible changes in substrate utilization toward lipids cannot be excluded.

Hypothermic Adaptation in Man

The diminished shivering response to the acute cold-tests reported in cold-acclimated or cold-acclimatized men is most frequently accompanied by a decline of heat production and a fall in body temperature (Wilson, 1966; Budd and Warhaft, 1966; Davis and Johnston, 1961).

A great deal was learned about the possible modifications that can develop in men living permanently in severe cold climates from studies carried out with various ethnic groups.

Nomadic Lapps, reindeer herders or hunters, who spend most of their life outdoors or in poorly heated quarters, were found to have metabolic rates during a cold night that were approximately 25% lower than those of control subjects (members of the research team) (Zeisberger and Brück, 1976). The most striking difference between the two groups, however, was the ability of the Lapps to sleep restfully for much of the night exposed to cold and to do so without marked shivering. The control subjects, on the other hand, awoke early, started shivering, and grew restless. Although the body core temperatures (T_{re}) of the Lapps measured before the night cold-test differed only slightly from those of the control subjects, it decreased to much lower values in the early morning hours, being at that time 0.8°C to 0.9°C below the T_{re} of the controls. Thus, the greater magnitude of body core cooling in the Lapps remains in agreement with their lower heat production.

Similar patterns of metabolic and thermal responses to cold were also described in the Negroid group from the Kalahari Desert (Wyndham and Morrisson, 1958) and in Australian aborigines (Hammel, 1964). Members of the primitive Australian tribe, who are also called Stone Age people (Folk, 1974), customarily sleep unclothed on the ground, even when the ambient temperature falls below freezing. Their total heat production, measured during cold exposure, is the lowest of the Caucasians and other ethnic groups examined (fig. 9) and they tolerate moderate hypothermia fairly well.

Hypothermic-type cold adaptation occurs also in the Korean diving women. As was mentioned before, the amas experience the most severe form of cold stress that human subjects voluntarily tolerate (Doi et al., 1979). Most of them are able to remain in water at 29°C for 3 hr without shivering, despite a decrease in rectal temperature below 36°C. Nondiving Korean women, with a comparable fat thickness, shiver in colder water than 32°C-33°C at the time when their body core temperature is about 36.5°C (fig. 10). Thus, the amas are able to maintain a greater temperature gradient between body core and body surface (6.8°C for the amas, 4.4°C for nondivers). A decreased shivering threshold temperature, accompanied by a reduction in the magnitude of thermal discomfort and cold sensation explain the high cold tolerance in the amas (Macari, Dauncey, and Ingram, 1983).

Alacaluf Indians of south Chile, living in primitive conditions in a climate characterized by cool, wet weather, present a slightly different example of cold adaptation from those described above. The Alacaluf Indians had the highest rate of heat production when exposed to the cold-night test of all the compared groups which, similarly to the Australian aborigines, does not undergo any changes with lowering of skin temperature. However, in spite of the lack of the metabolic response to cold, they remain normothermic throughout the night (Elsner, 1963). Thus, this ethnic group does not resemble either Caucasians or Australian aborigines.

Insulative Adaptation to Cold in Man

Members of polar expeditions usually develop a thicker layer of subcutaneous fat in winter than in summer (Zeisberger and Brück, 1976). However, this change is more likely caused by some factors other than cold exposure, for example, less physical activity or a modified diet, and as such cannot be considered an indicator of cold-adaptation; nonetheless, its consequence is an increased tolerance of cold. So far, the only example of a preferential laying down of a substantial amount of subcutaneous fat that can be directly related to cold acclimatization is the channel swimmers (Pugh and Edholm, 1955).

Changes in heat conductance, brought about by a prompt, intense, and sustained peripheral vasoconstriction were demonstrated by Budd and Warhaft in men exposed to a standard cold stress after a year spent in Antarctica (Budd and Warhaft, 1966). The enhanced vasoconstriction, accompanied by a heat exchange between arterial and venous blood made more efficient by acclimatization, significantly increases the insulating effectiveness of tissue. A result is a reduced need for greater heat production.

It should be emphasized that even slightly decreased energy expenditure on cold exposure is of importance from the point of view of a large total cost of acclimatization to cold, particularly in malnourished people (Folk, 1981).

Acclimatization to Local Cold Exposure

The hands and faces of men living in cold climate or working at low ambient temperatures are exposed to cold much more often than parts of the body protected by clothing.

It was proved that people who habitually expose their hands to cold–for example, Eskimos (Miller and Irving, 1962), Arctic Indians (Elsner, Nelms, and Irving, 1960), fishermen (LeBlanc, 1975; Krog et al., 1960), workers who fillet fish (Nelms and Soper, 1962), and lumbermen (LeBlanc et al., 1976)– respond to local cooling of the hands with much less pronounced cutaneous vasoconstriction, and with more rapid onset of vasodilation than occurs in unacclimatized men. Thus, they tolerate cold-stress better than men unadapted to cold.

In the standard test in which the hand is immersed in cold water, skin temperatures of the hands of Polish lumbermen decreased by 10.7°C, whereas those of the controls dropped 17.7°C. This indicates an increased blood flow through this area at the expense of the doubled heat loss from the cooled hands of the lumbermen (unpublished data).

Because of the above described changes, cooling the hands of acclimatized men causes less discomfort or pain and the hands maintain their manual capacity. Thus, acclimatization to the local cold exposure reduces numbness and preserves manual dexterity, thus protecting the hands from cold-related injuries.

Acclimatization to the local effect of cooling leads also to some substantial changes in the cold-induced activation of the sympathetic nervous system. Both in the Eskimos and in the Caucasians acclimatized to local cooling, the increases in the systolic and diastolic blood pressure are markedly reduced (LeBlanc, 1975).

CARDIOVASCULAR RESPONSES TO HAND AND FACE COOLING

Local cooling of the hand (e.g., cooling induced by immersion of the hand into cold water) causes a marked activation of the sympathetic nervous system, as evidenced by a reflex cutaneous vasoconstriction accompanied by an increase in heart rate (HR) and a prompt elevation of blood pressure, coinciding with sensation of pain.

Similar changes in diastolic and a more pronounced increase in systolic blood pressure also occur during local face cooling. However, contrary to the hand-cooling results, there is a decrease instead of an increase in heart rate, pointing to the enhanced vagal activity, by a reflex mechanism initiated most probably by stimulation of the trigeminal nerve endings. Thus, face-cooling activates both the sympathetic and parasympathetic nervous systems, as evidenced by elevations of blood pressure and slowing heart rate, respectively.

The beneficial effect of bradycardia, triggered by exposure of the face to cold, is questionable. Moreover, in some cases, for example, in patients with coronary insufficiency, such a response could have a deleterious effect, since the marked increase in blood pressure at a time when HR is decreased might impose an additional load on the heart, producing ischemia. Indeed, cardiac patients often experience pain when their faces are exposed to severe cold, and it seems likely that this pain may be related to bradycardia.

Cardiovascular responses to local hand and face cooling vary with physical fitness, sex, and the general thermal state of individuals (LeBlanc et al., 1978; Caputa and Cabanac, 1979). They can be greatly modified by cold adaptation.

MAN IN COLD WATER

Cooling Properties of Water

The temperature range in which man can stay in water without incurring excessive cooling is very narrow compared with that of air. This is a result of the physical properties of water. The thermal conductivity of water is about 25 times greater and the volumetric specific heat of water under normal conditions is about 4,000 times greater than the respective values of air (Keatinge, 1967; Glickman et al., 1967). Thus, a nude man will have difficulties in reducing heat loss enough to prevent body cooling even in water at a relatively moderate temperature (20°C-25°C). The aquatic environment can cool the body very rapidly, and the cold stress easily becomes so severe that it may be life threatening. It has been fully recognized, documented, and convincingly described by Keatinge in 1969 that in the dramatic sinkings of large passenger ships–the Titanic in 1912, the Andrea Doria in 1936, the Lakonia in 1963–and fighting ships of World War II, hypothermia, caused by water immersion for a few hours, was primarily responsible for most of the deaths. The recent upsurge in aquatic sports in coastal waters and inland lakes has increased the risk of hypothermia from sudden immersion in cold water.

Survival time for men in water depends mainly on the temperature of the water. Hayward et al. derived an equation that predicts the survival time of an average sized adult supported by a life jacket in water of a given temperature:

$$t_s = 15.0 + 7.2 \, (0.0785 - 0.0034 \, T_w)$$

where t_s is survival time in minutes and T_w is water temperature in °C (Hayward, Eckerson, and Collis, 1975).

However, the survival time of human beings accidently immersed in cold water is highly variable among individuals. The thickness of subcutaneous fat is the most important factor determining the variability in cooling rate, since fat acts as a layer of body insulation. Fatter individuals have considerably lower core-to-skin conductances in the cold than do lean persons. A nude man of average body build will develop hypothermia after approximately 20-30 min in water at 5°C, and after about 1.5-2.0 hr in water at 15°C. An extra 1 mm of subcutaneous fat may be equivalent to increasing the water temperature by 1.5°C (Pugh and Edholm, 1955). An obese person cools at a markedly slower rate than a lean one, and the difference can be a matter of life and death in emergencies in the water.

Because of some extra fat that they usually have, women would be expected to survive longer in cold water than men. Swimmers, particularly channel swimmers, who endure long periods in cold water usually weigh more than other athletes of similar height and age because a higher percentage of their body weight consists of fat (Pugh and Edholm, 1955).

There are suggestions that the insulative layer of subcutaneous body fat develops as an adaptation to frequent and prolonged immersions in cold water. However, it does not seem to be a general phenomenon. The Korean amas, who make their living by regularly entering cold water, have less fat than other Korean women and much less fat than American women (Keatinge, 1967).

Thermal Balance during Cold Water Immersion

An increase in heat production by shivering or by voluntary muscular activity makes little contribution to the maintenance of thermal balance in cold water. During muscular contractions, muscle blood flow is markedly increased resulting in higher heat conductance to the skin and in enhanced whole-body conductance. This, in turn, elevates heat loss by an amount proportional to the difference between body-core and water temperature.

In addition, heat loss by convection, which is practically the only means of heat exchange in water, more than doubles as a result of the increased water turbulance created by body movements during swimming (Nadel et al., 1974; Holmer, 1974).

In general, exercise performed in water has an adverse effect on body thermal balance. In water at 5°C-15°C, the rate of cooling in swimming subjects is approximately 35%-50% higher than that predicted for motionless subjects (Hayward, Eckerson, and Collis, 1975).

On the other hand, men who were asked to work as hard as possible in cold water showed smaller decreases in body temperature than when they worked at a moderate intensity. This finding is easily explained since work at a faster rate can increase the rate of heat production more than that of heat loss in cold water. This is because hard exercise is associated with little further increase in muscle blood flow and only a slight enhancement of whole-body conductance.

However, maximal work can be performed for only a limited time (Nadel, Holmer et al., 1974). Thus, swimming in 18°C water at submaximal rate requires 0.5 liters of O_2 per minute more than swimming at the same rate in water at 26°C, thereby causing more rapid exhaustion or even collapse.

Children particularly should be made aware of the danger connected with swimming in cold water. The large surface area of the skin per body mass, especially in a lean child, facilitates heat loss from the skin to water; as a result, the lean child cools very rapidly when swimming in water at 20°C (0.05°C-0.10°C·min^{-1}) and his core temperature may drop quickly to 34.4°C-34.9°C (Bar-Or, 1980). Swimming in 20°C water is common in many regions of the world. Although it carries little risk of hypothermia for an experienced adult swimmer (because of a better cold-perception mechanism, which forces an adult out of water, it may present a risk for small, lean, overly ambitious young swimmers, who have not developed this mechanism of cold defense (fig. 11).

EFFECT OF COLD ON WORK PERFORMANCE

Most of the studies of the effect of cold on work performance have been performed under conditions of body-core, muscle, and skin temperatures reduced by various cooling procedures (Nadel, et al., 1974; Smith and Brück, 1981; Davies et al., 1975; Bergh and Ekblom, 1979; Bergh, 1980; Blomstrand et al., 1984). Thus, the results obtained and the conclusions reached reflect in fact responses of more or less hypothermic man to exercise, which may differ from those found when the increased heat production, due to shivering, has prevented development of hypothermia (Kaciuba-Uscilko et al., 1975).

Dynamic Exercise

Physical performance during dynamic exercise of short duration is reduced by 4%-8% for each °C of change in deep-body temperature, which coincides with a reduction in the maximal aerobic power ($\dot{V}_{O_2}$ max) by approximately 10% and a decrease in the maximal muscle strength, the former being most likely a result of the lowered exercise heart rate. The decrement in the peak heart rate has been mainly attributed to a direct effect of hypothermia on the cardiac muscle (Davis et al., 1975; Bergh and Ekblom, 1979), resulting in prolongation of the time to peak tension and of the relaxation time. The reduction in HR during maximal exercise performed at subnormal body temperature probably leads to a reduced maximal cardiac output, since the stroke volume remains unchanged (McArdle et al., 1976).

The reduction in performance cannot be attributed either to changes in the ratio between aerobic and anaerobic energy yield or to a diminished lactate production (Blomstrand et al., 1984). However, a higher muscle lactate content and the later appearance of peak blood lactate concentration, demonstrated in men performing heavy exercise at subnormal deep-body temperature, indicate a lower flux of lactates from muscle to blood, with resulting increased acidity of the working muscles. This effect may add to other negative influences of low body temperature (e.g., a decreased muscle contractility), thus contributing to the decrement of physical performance.

The energy cost ($\dot{V}_{O_2}$) of submaximal exercise (150 W) performed by human subjects with body-core temperatures below 36°C (Bergh, 1980) is increased above normal levels, the increase being the highest at the lowest mean skin temperature. This indicates that a greater relative load is placed on an individual exercising at subnormal body temperature. The extra oxygen uptake is attributed to the metabolic cost of shivering. The increase in $\dot{V}_{O_2}$ with lower body temperatures is not accompanied by a

concomitant elevation of HR, which is often even reduced at a given submaximal work load. The reduced HR cannot be explained by a diminished sympathetic activity, since the plasma noradrenaline (NA) concentration is usually much higher at low body temperatures than it is at normal body temperatures, both at rest and during physical exercise. It is possible, however, that the effects of NA on beta-adrenergic receptors are reduced since beta-adrenergic blockade, applied under these conditions, does not further reduce heart rate, as is the case at normal body temperature.

A prediction of physical work capacity on the basis of HR measurements during submaximal exercise performed at lowered body temperature may lead to an overestimation of physical work capacity (Bergh, 1980). Moreover, because the hypothermic subjects are not aware of the increase in their relative work load and of their reduced potential for heavy exercise, some severe strain may occur.

A small decrease in deep-body temperature (by about 1°C) before starting exercise does not diminish the submaximal performance. On the contrary, some lowering of body temperature before such exercise may even have a beneficial effect, since the onset of sweating occurs at higher work loads and the cumulative sweat secretion is considerably smaller (fig. 12) after pre-cooling, thus indicating less thermoregulatory effort (Smith and Brück, 1981). No significant differences were found in the steady state $\dot{V}_{O_2}$ and hemodynamic responses to 30-min of exercise at moderate intensity performed at low (5°C) and room (20°C ±2.0°C) temperatures. During the exercise preceded by a short-time (30 min) rest in a cold (5°C) room, the normal increases in body temperature were delayed and the highest blood noradrenaline, adrenaline, and FFA concentrations were reached, indicating that the effects of cold exposure and exercise on these variables can be additive (Kaciuba-Uscilko et al., 1975).

Isometric Exercise

Maximal isometric strength was found to be only slightly affected (2%/°C), and endurance for isometric exercise was even improved at subnormal muscle temperatures (Edwards, Harris et al., 1972). On the other hand, force development under these conditions was reported to be attenuated (Asmussen, Bonde-Petersen, and Jorgensen, 1976). The effects of cold on human responses to isometric exercise are far from fully evaluated. Under conditions of the above cited studies local cooling of limbs induced only small changes in body-core and skin temperatures, thus resulting in a minimal shivering response.

It seems most likely that severe shivering would interfere with coordination of movements, causing a further increment in the major function.

HYPOTHERMIA

It has been mentioned earlier that severe hypothermia is the principal cause of many casualties that result from accidental, and in some instances voluntary, water immersion (Keatinge, 1967; Maclean and Emslie-Smith, 1977; Holmer and Bergh, 1981). Hypothermia is also a major factor in Antarctic diving operations (Dick, 1984).

The lethal lower limit of the human body-core temperature lies within the range of 23°C-25°C. A few exceptions have been reported in which core temperature dropped between 9°C and 18°C and in which the victims survived deep hypothermia after careful rewarming in a hospital (Keatinge, 1967).

Clinical Symptoms

Sudden cooling of the skin causes a great increase in heart work, so the most damaging and diffuse effects of cold are on heart. With developing hypothermia the cardiac output declines, which is attributed to bradycardia, increased peripheral resistance, and a low stroke volume (Nicolas et al., 1974). In patients with core temperatures below 28°C atrial fibrillation often appears, sometimes accompanied by much more hazardous ventricular fibrillation. The latter is probably brought about by an insufficient supply of oxygen for myocardial metabolism.

The cerebral activity responsible for consciousness is not readily disrupted by hypothermia, although after some time in this state the cerebral blood flow declines because of the reduced cardiac output and arterial blood pressure, as well as a rise in blood viscosity. In severe cases, there is circulatory arrest of the brain and death results within less than 1 hr.

Mental impairment, leading to confusion and delirium, is most probably one of the major factors contributing to death from hypothermia on prolonged cold-water immersion, since persons in this state act in ways that limit their chances of survival. In addition, other effects of severe hypothermia on body functions–segmental pulmonary collapse, hepatocellular damage, renal impairment, and disturbances of acid-base equilibrium–may also affect the hypothermia victim's chance for survival.

In the management of hypothermia, different methods of warming the patient (e.g., slow-spontaneous or rapid-active) have been used depending on the severity of the condition, prevailing symptoms, and age of the patient, as well as on the presence of medical staff and the availability of necessary equipment. In some severe cases of hypothermia oxygen administration, electrical defibrillation, and intravenous infusion of fluids and electrolytes are necessary.

Accidental Hypothermia in the Elderly

Accidental hypothermia, with deep-body temperature below 35°C, is one of the hazards of old age, even in apparently fit individuals (Maclean and Emslie-Smith, 1977; Collins et al., 1977). Elderly people, often living and sleeping in unheated or poorly heated rooms, can lose excessive heat to the cold air; however, their ability to compensate for the increased heat loss is substantially less than that of younger subjects (Robertshaw, 1981). When fuel costs rise and energy-conservation measures are made more extreme, hypothermia-related deaths can be expected to rise among the elderly during winter (Besdine, 1979).

One of the main problems of temperature regulation in the elderly is their reduced sensitivity to changes in temperature (Collins et al., 1977). Whereas young persons can perceive mean temperature differences of 0.8°C ±0.2°C, elderly subjects (69 to 90 years) can discriminate a mean temperature difference of only 2.3°C ±0.5°C. Moreover, an analysis of ambient temperature preferences in elderly people revealed that the range of air temperatures they described as "slightly warm" was 11.8°C to 19.5°C, whereas the equivalent range for young people was 15.3°C to 28.0°C. Since conscious temperature perception triggers behavioral responses and autonomic control of temperature regulation, less sensitive perception may easily lead to thermolability and to hypothermia.

In addition, equal exposure to cold induces a greater drop in body-core temperature in the elderly than in the young. The difference may be attributable to a defect in the thermal effector mechanisms of the

elderly. It is known that elderly subjects are less able to prevent heat loss by vasoconstriction and that their metabolic response to cold is delayed and of reduced magnitude (Robertshaw, 1981; Collins et al., 1977).

The maximal metabolism in response to cold has not been studied in elderly people. However, the decreases in BMR and in the maximal oxygen uptake ($\dot{V}_{O_2}$ max) with age suggest that the maximal increase in metabolism achieved by shivering might also be reduced (Robinson et al., 1976).

It is possible that hypothermia in the elderly is associated with malnutrition and a resultant reduction in subcutaneous fat and tissue insulation, or with other dietary deficiencies (e.g., reduced protein intake) that may limit specific dynamic actions of food.

Accidental hypothermia in the elderly population will cease to be a common problem only when they all live in comfortable, warm surroundings at ambient temperatures of at least 21°C. Until this ideal is reached, doctors, nurses, and relatives taking care of older people should be aware of the risk that environmental cold poses for them (Irvine, 1974).

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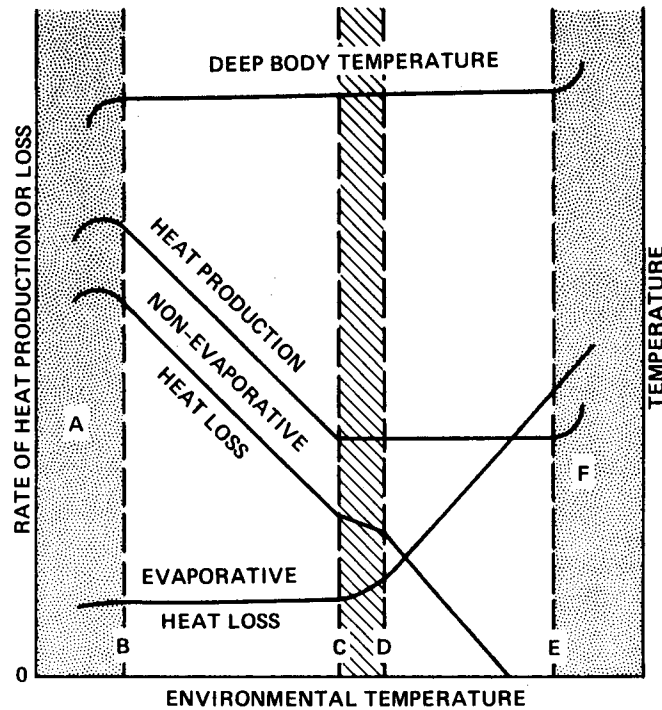
Figure 1.– Relationships between heat production, heat loss (evaporative plus nonevaporative) and deep-body temperature in a homeothermic organism subjected to different environmental temperatures. (A) zone of hypothermia; (B) temperature of summit metabolism and incipient hypothermia; (C) critical temperature; (D) temperature of marked increase in evaporative heat loss; (E) temperature of incipient hyperthermal rise; (F) zone of hyperthermia; (CD) zone of least thermoregulatory effort; (CE) zone of minimal metabolism; (BE) thermoregulatory range (from Stanier, Mount, and Bligh, 1984).
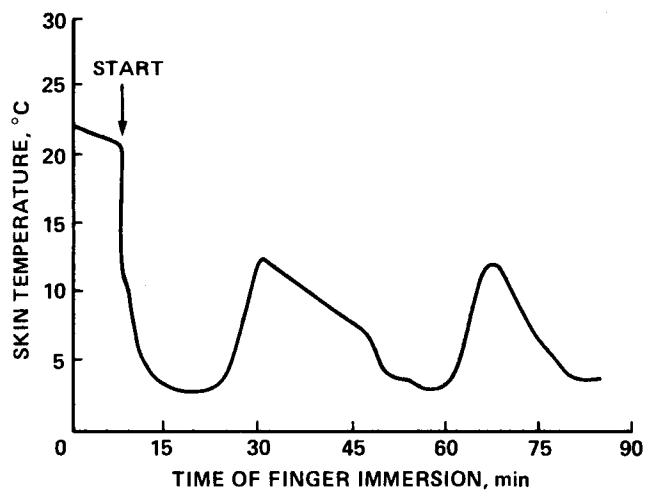
Figure 2.– Changes in finger skin temperature following immersion of a finger in ice water: hunting phenomenon (from Lewis, 1930)

33
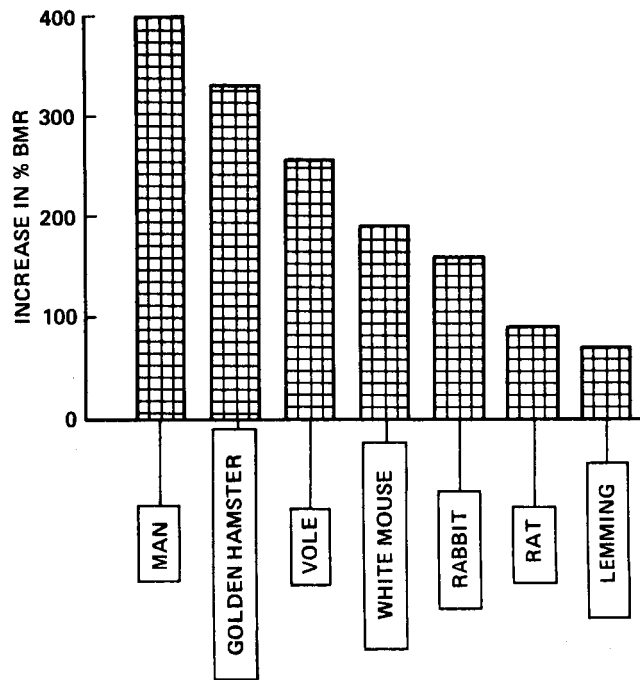
Figure 3.– Capacity of heat production by shivering, expressed as an increase in the basal metabolic rate (BMR) in different mammalian species (from Jansky, 1965).
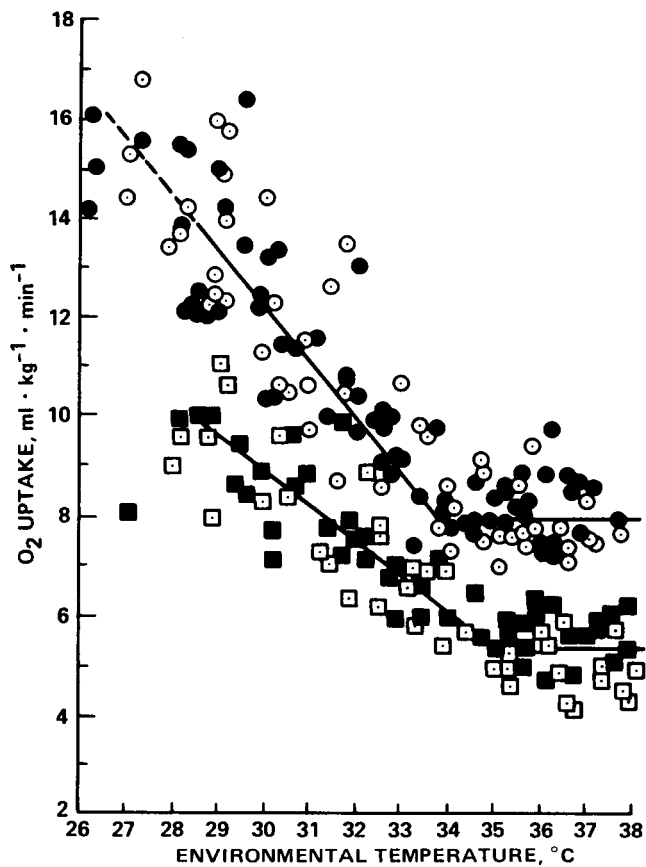
Figure 4.– The relationships between environmental temperature and oxygen uptake in babies 4-12 days old (lower curve) and 9-11 days old (upper curve). Black marks indicate the data obtained from babies who were more than 25% below average weight at birth (from Hey, 1969).
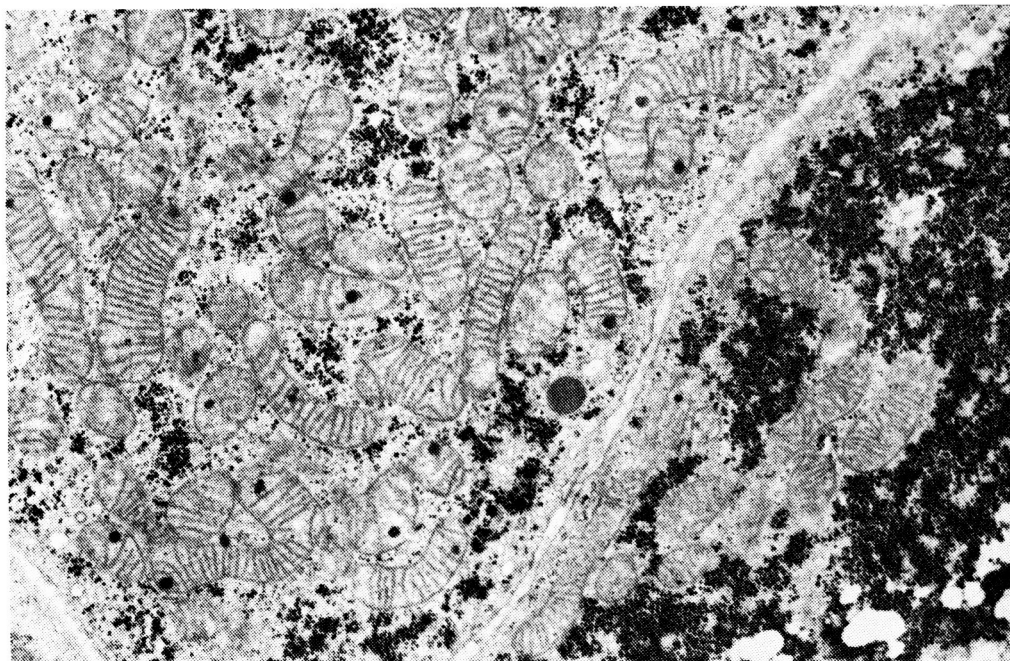
Figure 5.– Electron-microscopic section of intrascapular brown fat (courtesy of Dr. Gisela Schneider-Picard).
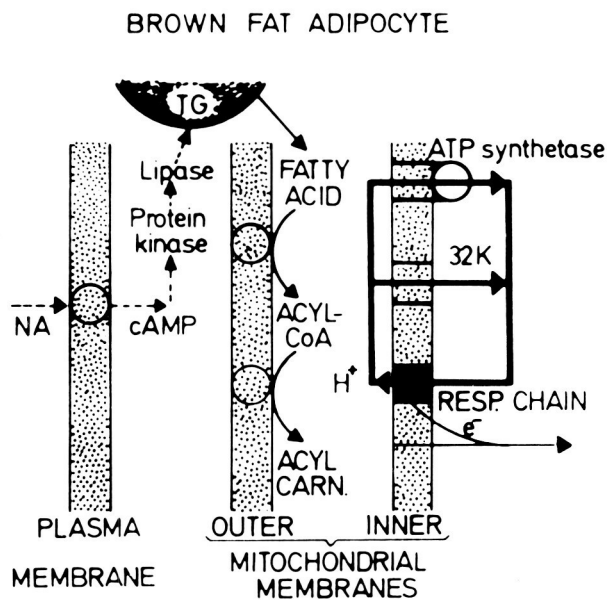
Figure 6.– A model of metabolic events occurring within the brown adipocyte (from Nicholls and Locke, 1984).
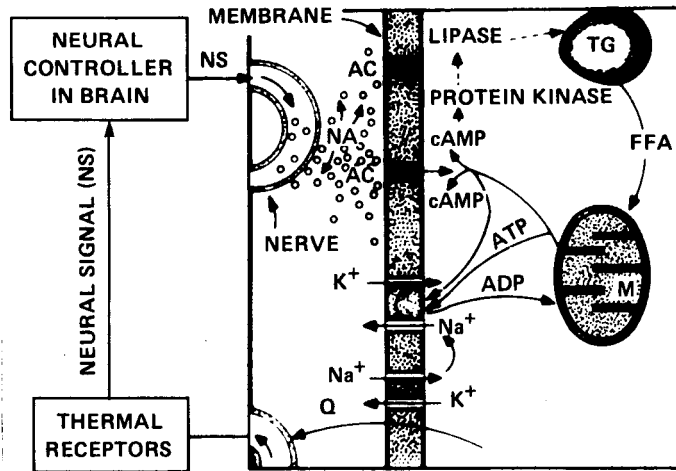
Figure 7.– A proposed model of the system controlling heat production in brown adipose tissue (from Horowitz, Fuller, and Horowitz, 1976).
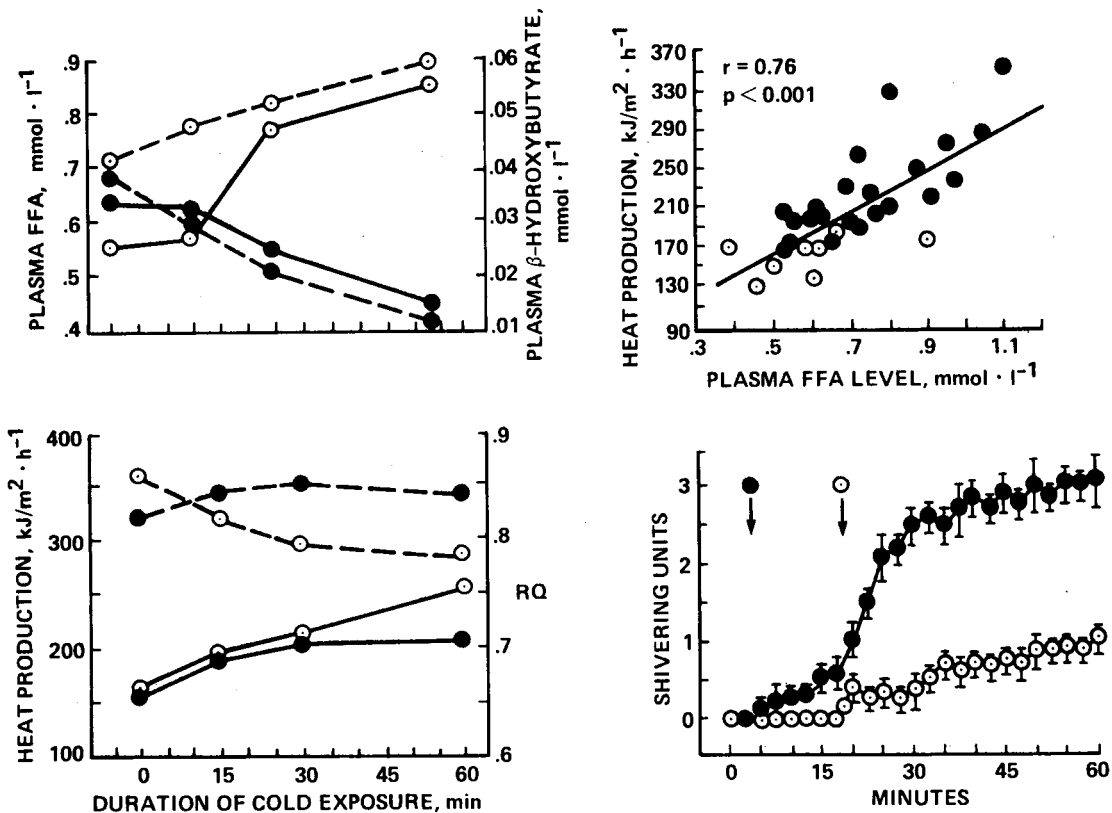
Figure 8.– Physiological responses to cold in young men from Hokkaido (Northern Japan) exposed to low ambient temperature without (open circles) and with (filled circles) an inhibition of the sympathetic nervous system by administration of nicotinic acid. On the upper right side of the figure a relationship between the plasma FFA level and heat production is presented (based on the data from Doi et al., 1979).
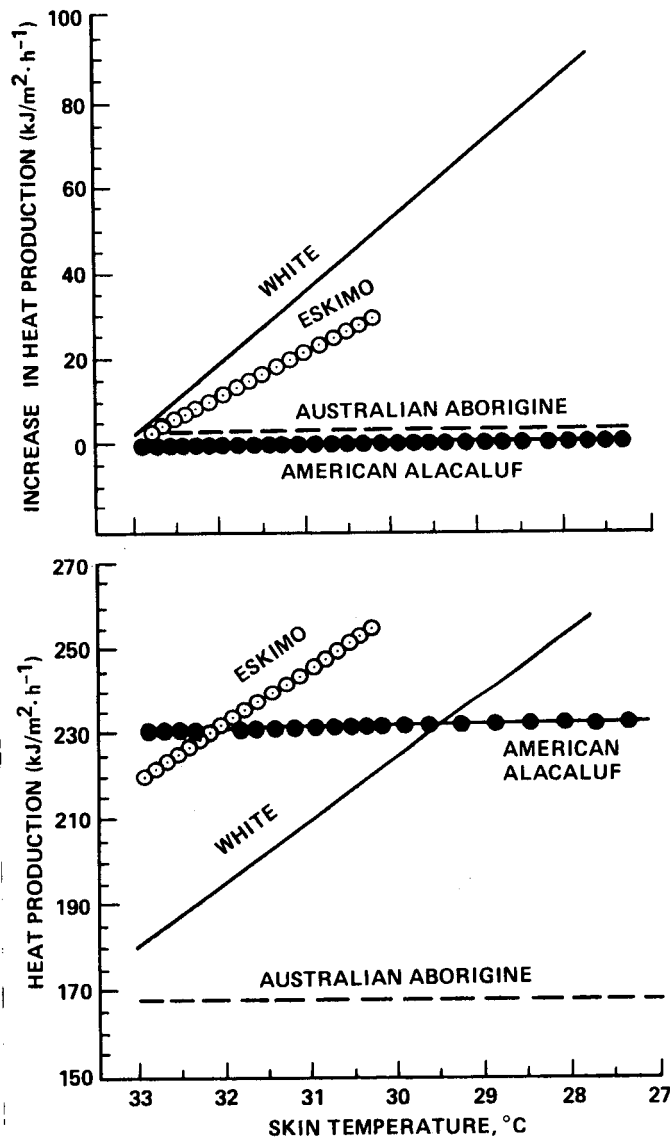
Figure 9.– Thermal responses to lowering of skin temperature in representatives of various ethnic groups (from LeBlanc, 1975).
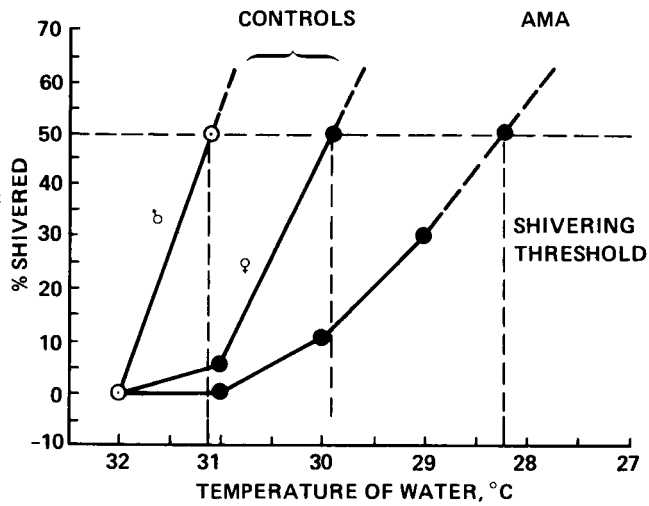
Figure 10.– Comparison of the shivering thresholds in control Korean women and men with those of Korean amas (from Hong, 1973).
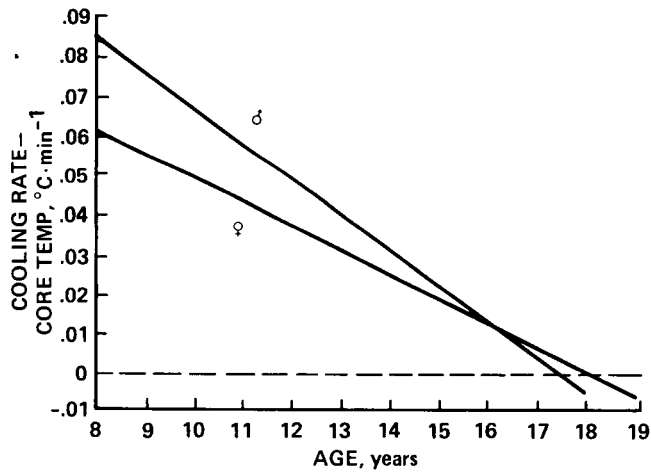

Figure 11.– Cooling rate, as measured by a decrease in body-core temperature, in relation to age of boys and girls swimming in water maintained at 20.3°C. No changes in core temperature occurred in adolescents, as indicated by the broken line (from Bar-Or, 1980).
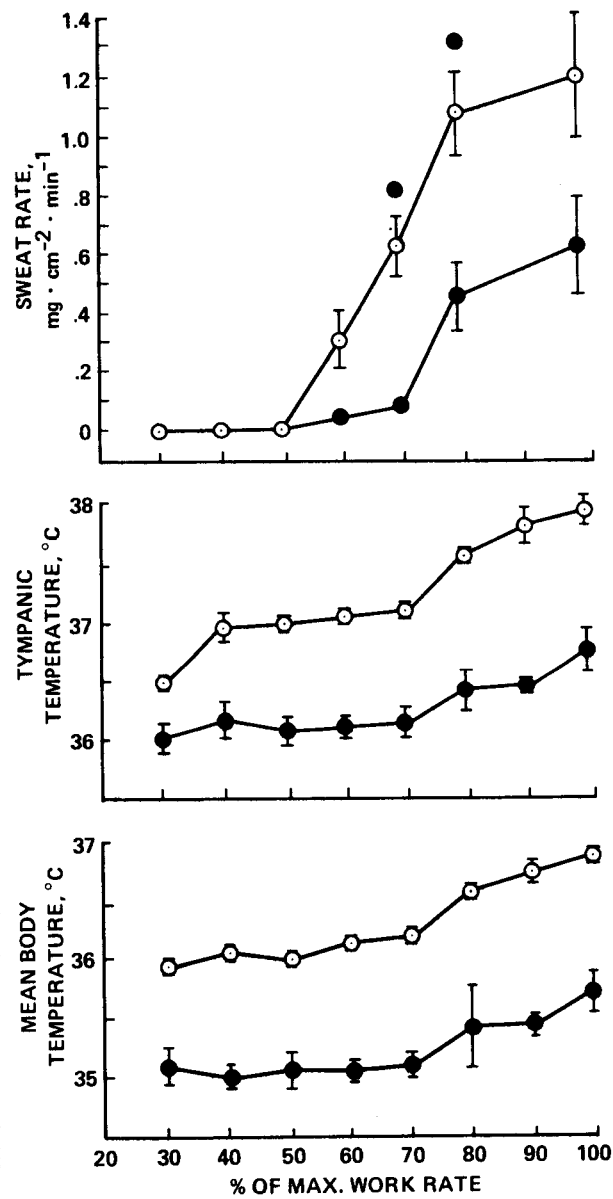
Figure 12.– Comparison of changes in body temperatures and the sweat rate in human subjects performing physical exercise with (filled circles) or without (open circles) precooling (from Smith and Brück, 1981).

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15. Supplementary Notes

Point of Contact: John E. Greenleaf, Ames Research Center, MS 239-17
Moffett Field, CA 94035 (415) 694-6604 or FTS 464-6604
*Polish Academy of Sciences, Medical Research Center, Department of Applied Physiology, 00-730 Warsaw, Poland

16. Abstract

This review focuses on the responses and mechanisms of both natural and artificial acclimatization to a cold environment in mammals, with specific reference to human beings. The purpose is to provide basic information for designers of thermal protection systems for astronauts during intra- and extravehicular activities. Hibernation, heat production, heat loss, vascular responses, body insulation, shivering thermogenesis, water immersion, exercise responses, and clinical symptoms and hypothermia in the elderly are discussed.

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