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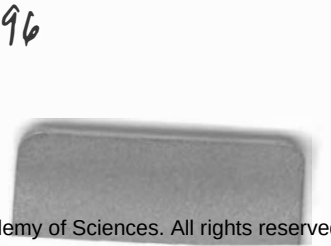

Polar Biomedical Research

An Assessment

Appendix: Polar Medicine—A Literature Review

Report to the
Ad Hoc Committee on Polar Biomedical Research
Polar Research Board
Commission on Physical Sciences,
Mathematics, and Resources
National Research Council

Prepared by
Frederick C. Koerner

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Preface

To guide the evolution of U.S. polar research during the next two decades, the Polar Research Board is issuing a series of reports on research needs and strategies. Studies in the series deal with, for example, marine ecosystems, the upper atmosphere and near-earth space, snow and ice, permafrost, climate, and biomedical research.

The study on polar biomedical research was undertaken by the Ad Hoc Committee on Polar Biomedical Research, chaired by Chester M. Pierce. Its objectives were to examine and summarize current knowledge of the medical aspects of life in polar regions and to consider research needs in relation to the expected increase in human populations in these areas as a result of growing economic, scientific, and military activities.

This Appendix to the report of the Committee reviews the current level of understanding in polar biomedicine, lists more than 700 references, and provides background for the discussion, conclusions, and recommendations in the Committee's report. The Committee believes that it will be a useful resource for administrators, researchers, providers of health care services, and others concerned with human health in polar regions.

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Introduction

This Appendix was developed as background for the study of the Ad Hoc Committee on Polar Biomedical Research, which presents recommendations to guide the evolution of this field over the next two decades. The information reviewed comes from the literature published in English since 1940.

In developing its report, Polar Biomedical Research: An Assessment, the Committee read thoroughly but not exhaustively. It consciously avoided studies based on experimental animals, studies of basic physiology, especially on the cellular, tissue, or organ level, and epidemiologic surveys of polar populations. It, of course, gave special attention to studies undertaken in polar zones. Most of the work cited was done when experimental design and data manipulation were not as rigorous as they are today; thus, conclusions based on the earlier work often have to be carefully evaluated. The Committee did not try to reconcile conflicting data, leaving that task for others with greater expertise.

The Committee hopes that this summary will serve as an introduction to the literature for those working in polar biomedical research and that it will also provide the reader with additional details and perspective on the discussion and recommendations in the main report.

Nutrition

A. Basal requirements

Early calculations[722] suggested an inverse linear correlation between environmental temperature and caloric needs. At -29°, baseline intake was estimated to be 5000 kcal/day. Subsequent studies conducted in polar regions[1-6] showed that caloric needs are the same as those in temperate and tropical zones--3000-3600 kcal/day for average activity. There probably is a 2% to 5% increase in needs because of the extra weight of heavy clothing,[7,8] and the muscular work of shivering increases caloric requirements.[9] Partition of calories to include a bedtime snack probably leads to higher rectal and toe temperatures and better sleep during the night.[10] The composition of the ideal diet is identical to a standard military diet (15% protein, 35% fat, 50% carbohydrate).[11] There is experimental evidence that high fat and high carbohydrate diets may improve heat conservation and psychomotor function in the cold.[12,13] Lower levels of serum ascorbic acid have been noted in men working outdoors,[14,15] but dietary supplementation (one gram a day) did not improve health.[16] Thus, no needs above the USFDA recommended minimum daily requirements of vitamins and minerals have been documented.[17] Studies of basal water balance have not been reported.

Note: All temperatures expressed using Celsius scale.

B. Requirements during work

Under field conditions diet planning is especially important. Again, caloric needs are related to activity and are not significantly greater than those of men in temperate zones.[18] Thus, for minimal activity, 1500 cal/m^2/day are required at -10° and 2000 cal/m^2/day are needed at an ambient temperature of -30°.[18] During heavy work in subarctic climates, needs as high as 6600 cal/day have been recorded.[11,19-24] Since negative calorie balance leads to lower rectal temperatures,[25] adequate caloric intake is critical. Even when enough calories are provided, however, there may be loss of fat and increase of muscle due to the conditioning effects of exercise.[20,22] There may also be a loss of body weight of 1-3 kg due to dehydration.[22,26,27]

C. Changes during starvation

During semistarvation (insufficient caloric intake) several changes ensue. There is rapid weight loss (8% in 5 days[18] and 12% in 14 days[25]) of which 10% represents loss of muscle, 40% loss of fat, and 50% loss of fluid.[18,28] This fluid loss may represent as much as 15% of the extracellular fluid volume, and tachycardia and hypotension can develop.[18] Water supplementation does not reverse this fluid loss, but sodium supplementation (100 mEq/day) does.[29-31] Carbohydrate and bicarbonate supplements may counter the ketosis of starvation, but a high fat and high protein diet does not.[31] Specific menus for a trail diet[32] and emergency rations[33] have been proposed.

Physiologic Changes during Polar Life

As people acclimatize to polar zones, environmental stresses evoke predictable changes in physiologic values. Although these alterations vary in magnitude among individuals, they are seen to some degree in most persons. Thus, the new levels probably represent the "normal" (or expected) values for men in these situations. The following changes have been elucidated. Many others probably exist.

A. Immediate responses

There are few reports of changes occurring soon after arrival in polar zones. Bly describes diuresis; hemoconcentration; eosinopenia; lymphopenia; and elevations of serum urate, phosphate, and potassium.[34] Catecholamine excretion increases sharply.[35] On arrival at high altitudes, minute ventilation and alveolar ventilation increase and dead space decreases.[36] Erythropoietin levels in serum and urine rise.[37] Stage 3, stage 4, and REM sleep decrease, and stage 1 and stage 2 sleep increase.[38]

B. Long-term responses

Most investigators have studied later changes. Blood pressure may drop,[15,39-41] but the drop is unrelated to changes in weight.[42] In one Antarctic study, the nadir of systolic pressure was 97 mm Hg in October.[39] Diastolic pressure may also fall to 68 mm Hg in September.[41] Data from other stations did not corroborate this, however.[36,43,44] The radial pulse slows to a range of 56-60 beats/minute in December (Antarctica[39,42]). The mean oral temperature was

36.1° and showed no consistent seasonal change.[42] Rectal temperature may remain unchanged[41,45] or may fall.[40] Body weight varies with activity,[26,27,42,46] but overall increases 1.5-3.0 kg/year.[26,27,43,46-48] Data from a base where persons were active all year showed no seasonal variation of body weight.[20] Changes in subscapular skinfold thickness paralleled changes in body weight after an initial decline,[27,41,42] probably due to physical conditioning.[47] The basal metabolic rate shows no variation.[49-51]

Sebum production is decreased, probably due to inhibitory effects of cold, wind, and decreased ultraviolet irradiation.[52] Palmar sweat gland activity decreases during the winter.[53] Nails may grow more slowly in the cold, possibly because of decreased blood flow.[54] Others have found normal growth rates.[55]

Persons living at the South Pole have shown the increases in forced expiratory flow rate, FEV_1, MVV, and minute ventilation. They have shown decreases in dead space, and the hypoxia, hypocapnia, and mild alkalosis associated with high altitudes. Tidal volume, alveolar ventilation, and FVC are unchanged.[36] Some persons gradually developed right axis deviation.[36] Rhinorrhea also occurs during work in the cold. It is due to condensation of water vapor as warm humid air is exhaled through the cold nasopharynx.[56]

Elevations of hematocrit have been seen in persons residing at high altitudes.[36,57] Decreases in neutrophils,[58] eosinophils, and monocytes[439] have been reported. Hemoglobin electrophoresis is unchanged.[36] The whole-blood clotting time has increased to a peak in September or October (Antarctica[39,59]). The prothrombin time may increase.

Seasonal variations in PBI,[51] thyroid hormone, cortisol, and growth hormone[61,62] have not been shown. There may be decreased tolerance to an oral glucose load during the winter.[62,63] Catecholamine excretion is increased during the cold months.[35,64] The circadian pattern of 17-hydroxycorticosteroid excretion depends on daily activity patterns.[64]

Although mean duration of sleep is unchanged,[65,66] sleep onset latency increases and the percent of REM sleep decreases. There is progressive loss of stage 4 sleep and diminution of stage 3 sleep.[67]

Many have observed a relative freedom from upper respiratory tract infections during isolation. Cameron prospectively studied a group of winter-over personnel

at Mawson Station.[68] There were no colds during the period of isolation, but a few men developed mild colds following contact with visitors. When the men returned to civilization, most had severe colds.[69] The significance of these findings is unclear, however, because Allen documented an outbreak of colds after 17 weeks of isolation.[70] Staphlococcus and streptococcus persist in the nose and throat[71] and mycoplasm in the genitourinary tract.[72] Under these crowded conditions viruses are easily spread.[73] Thus, a reduced number of colds is probably a manifestation of immunity to indigenous organisms and lack of exposure to new strains. The more severe colds on return suggests impaired immune function. Holmes claims that nasal immunoglobulin G concentration is reduced at the end of the period of isolation and that innoculation with rhinovirus RV2 produces more severe colds in Antarctica.[74] Levels of serum immunoglobulins (IgG and IgM) fall during the winter.[75] Lund, on the other hand, found no change in serum immunoglobulin E or reactivity of skin tests to common allergens.[76]

Serum total cholesterol has shown no change[39,77] and a peak in September (Antarctica[59]). During the winter, beta-lipoprotein cholesterol may increase as alpha-lipoprotein cholesterol falls. Sledging reverses these changes.[77] Phospholipids, triglycerides, and cholesterol esters are unchanged.[77]

C. Adaptive responses (acclimatization)

Although well established in experimental animals, acclimatization of man to cold environments is a controversial issue. Anecdotal evidence suggests that it does occur. Researchers have attempted to address this problem by studying Australian aborigines,[75-80] Bantus,[81,82] Kalahari bushmen,[83-85] Gaspe fishermen,[86,87] Lapps,[88-90] Eskimos,[84,91-108] Korean diving women,[109,110] and other populations assumed to be adapted to cold. These groups demonstrate two types of responses to a cold stress. Populations such as Australian aborigines maintain metabolic rates at basal levels, thus skin and core temperature fall. Other people (Caucasians, Eskimos, Lapps) increase their metabolic rate to maintain rectal and skin temperatures near normal. Although such differences have been documented, it is difficult to be certain they represent physiologic adaptation rather than cultural differences.

Others[8,111-118] have studied changes during experimental cold exposure. The data are conflicting, but it seems that following generalized cold exposure, rectal temperature rises[112,114] and skin temperature drops below control levels. During the subsequent days, skin temperature rises,[114,116,119] rectal temperature may fall[113,115] (or may not,[8,112]), shivering decreases,[114] and oxygen consumption falls. Repeated cold exposure may lead to lower body temperatures,[111, 115,120] higher skin temperatures,[117] less shivering,[115,120] and less oxygen consumption[120] during a cold stress. These changes may represent cold acclimatization, but physical training leads to similar changes.[111,121,122]

Repeated cooling of the hand may lead to a higher resting skin temperature,[123] and during cold water immersion altered vascular responses may lead to earlier onset of CIVD[124] and faster cycling times and rewarming rates.[125] Other data, however, show that repeated cooling of one finger did not alter vascular responses during cooling; it did reduce the associated tachycardia and pain.[126] This suggests that central habituation rather than local adaptation is responsible for altered responses.

There have been few studies of human acclimatization in polar regions.[23,40,41,45,48,121-123,127-147] Resting metabolic rate is unchanged.[49-51,145,146,148] Cold stress may be handled more effectively (skin and rectal temperatures maintained at higher levels,[40,48, 121,128-130]), but the data are conflicting.[41,45,127] Excretion of 17-hydroxysteroids and 17-ketosteroids during an experimental cold stress may be more pronounced in Antarctica. The hypertensive response to norepinephrine is reduced after several months.[143,144] Men may wear fewer layers of clothing on the trunk[134, 142] and hands,[135,136] but the data are again conflicting[135,149] and difficult to interpret. After several months, the resting skin temperature,[137,140] blood flow,[141] and heat loss[140] of the hands may decrease. Increased resting finger temperatures have been reported, however.[123] During cold exposure, finger temperatures may be higher[123] and numbness less than control levels.[123,137]

Thus, there probably is adaptation of the hands to cold exposure as manifest by less numbness and clumsiness and higher skin temperature. More general changes in metabolic response to cold probably do not occur.

Although Budd has demonstrated limited cold stress during sledging[23] and thermal discomfort during outdoor station work,[138] Norman's data indicate little thermal stress during mundane life.[139] Similarly, the subclothing trunk-skin temperatures of Lapps range between 31° and 34°.[88] It seems therefore that most human acclimatization to polar life is achieved through technologic maneuvers rather than physiologic adaptation.[85,150,151]

Pathologic Changes during Polar Life

Life in the polar zones entails increased risks for diseases as diverse as scurvy and carbon monixide poisoning.[152-162] Perhaps the most obvious are local and systemic cold injuries.

A. Local cold injury

Originally trench foot, immersion foot, shelter foot, frostbite, and other forms of local cold injury were considered to be distinct entities occurring through different mechanisms. It is now felt that vascular changes and tissue hypoxia are responsible for all types of local cold injury and that variation in the clinical features reflects variation in the nature of the insult and the host responses. The pathophysiologic mechanisms have been summarized.[151,163-165]

As tissue cools, several mechanisms decrease tissue perfusion and thereby reduce heat loss.[166] Cold causes direct[167-169] and local[169] reflex constriction of muscular arteries[170-172] and veins,[167] thus decreasing local blood flow.[173,174] If hypothermia is present, central reflexes further decrease blood flow.[90,103,174-177] Relaxation of arteriovenous sphincters diverts blood from capillaries.[167,168,171,178,179] The nadir of blood flow is usually in the range of +10° to -20°.[176,177,180,181,182] Below - 20°, there is intermittent intense cold-induced vasodilatation (CIVD).[169]. The mechanisms involved are not understood, but blood flow increases to a normal level and the tissue temperature may rise 20° to 30°.[183] The phenomenon may be due to intermittent paralysis of vasoconstricting sympathetic fibers controlling arteriovenous sphincters.[169] (Flow

through the digital arteries is unchanged by CIVD.[170]) The intensity of CIVD varies among anatomic sites. Regions such as the nipple, scrotum, lateral arm, sole, popliteal fossa, and thigh show no response.[184] Despite the increase in tissue temperature, CIVD does not alter the time course of cooling between cycles.[185]

As a result of these changes, heat loss is reduced at the expense of intermittent ischemia. If the tissue is cooled only briefly and warmed rapidly, this ischemia is tolerated and no damage results. If, however, the cold stress continues, additional changes further compromise tissue perfusion. Endothelial cells are damaged by cold, rendering capillaries leaky.[178,186-189] Transudation of plasma leads to erythrocyte clumping[167,188,190-192] and edema formation.[191,193] Changes in the rheologic properties of blood increase its viscosity[194,195] and favor erythrocyte aggregation.[196-198] Histamine release may also contribute to edema formation.[199] These changes in the microcirculation coupled with increased binding of oxygen to hemoglobin[200,201] make cell survival precarious between 5° and 15°.[202] In this range, cellular metabolism continues; but as oxygen delivery lags behind oxygen demand ischemia develops. The degree of damage depends on the temperature and exposure time. Gangrenous necrosis has been seen following temperatures as high as 18° with an exposure time of several days. Lower temperatures have correspondingly shorter critical times. The important point, however, is that damage occurs because metabolic demands outstrip vascular supply. Severe damage and tissue loss may be seen without freezing.[203]

Human tissue freezes between -0.53° and -0.65°,[204] although it can supercool to lower temperatures. When freezing occurs, direct cell toxicity may contribute to injury.[205-207] (Below 5° ischemic damage is slight; cellular metabolism is minimal and oxygen utilization is less than oxygen delivery.) This toxicity is probably due to intracellular dehydration, because water crystallizes during freezing.[208] Mechanical disruption of cell organelles by ice crystals may also play a role.[202] It is important to stress, however, that even when tissue is frozen solid, most of the tissue damage is due to the ischemia that occurs before freezing and just after thawing.[209]

In summary, the various cold injury syndromes represent arbitrary points on a continuum of cold injury. Trench foot, immersion foot, and shelter foot result from nonfreezing vascular damage and resultant ischemia. There is usually no tissue loss, but gangrene can be seen in severe cases. In frostbite, high altitude frostbite, and other forms of freezing cold injury, vascular damage is more severe, and in addition there may be direct cell damage. Again the outcome varies from complete resolution to gangrene. The exact clinical manifestations and course of a cold injury thus reflect variations in the temperature, exposure time, and host factors rather than different pathophysiologic mechanisms.

Other effects of local cold exposure include impairment of manual dexterity,[210-214] partly due to joint stiffness[215] from increased viscosity of synovial fluid.[216] Impaired muscle contraction also probably contributes.[213,214,217,218] Tactile discrimination[214,219,220] and vibratory sensitivity[221] decrease as skin temperature falls. The effects of these changes on performance in the cold has been reviewed.[222]

There are several reviews dealing with clinical features of cold injury.[164,179,202,223-249,310] Clinical and experimental data suggest that hypoxemia, anemia, immobility, moisture, wounds in the same extremity, dehydration, cigarette smoking, blood group 0, previous cold injury in the same extremity, dark skin, and birthplace in a warm climate all predispose to cold injury.[227,228,241,250-256,726] Alcohol intoxication (aside from its effects of impairing judgment) does not seem to be a risk factor.[241,242]

The signs and symptoms encountered during the course of a variety of types of cold injuries have been described, and some papers include many photographs.[179,228,230,245,246] Immediately after warming, the skin is cool and mottled. Pulses are often decreased, and capillary filling is sluggish. In mild cases the patients complain of hyperesthesia of the affected skin. With more severe cases there is anesthesia. Two to five hours later the skin in the distribution of the injury becomes flushed, hot (30° to 35°) and dry (due to anhydrosis). Anesthesia gradually gives way to hyperesthesia. Burning or throbbing pain develops. It usually peaks at 48 hours and may persist for many weeks.

Muscles of the exposed area are often weak. (These signs and symptoms are probably due to damage to peripheral nerves.[257]) Edema accumulates and vesicles form. With mild cold injury, vesicles form within 24 hours, and their rapid appearance indicates the likelihood of no tissue loss. In cases of more severe injury they may not appear for 3 to 7 days or may not appear at all except at the line of demarcation of vital tissue. New shooting pains may develop after 7 to 10 days. They may last for several months and may recur even later. During the several weeks following injury, vesicles and adjacent nonvital tissues dry, harden, blacken, and slough. With severe damage this may take months and entire digits or distal extremities may be involved. During this stage the nonvital tissue is usually not tender. The skin surrounding and underlying the gangrenous areas will be red, thin, tender, and sensitive to cold. As peripheral nerves regrow, sensation, sweating, and strength return and pain diminishes.

In the immediate care of cold injury, it is critical that the tissue not be thawed and refrozen.[246] It is probably better to allow tissue to remain frozen until such time that definitive therapy can be instituted than to thaw it under field conditions if there be any chance of refreezing before proper therapy is available. Remarkable salvage can be obtained in the former situation, while the latter almost guarantees tissue loss. Frozen and recently thawed tissue is fragile and must be protected from mechanical trauma. Rubbing, pressure, and chafing disrupt tissue and increase tissue loss.

When definitive therapy is instituted, rapid rewarming improves tissue salvage.[179,241,242,245,246,258,259,261-265] Therapies such as gradual thawing, cold,[266,267] and rubbing with snow only prolong the time spent below 15°, leading to further ischemia and cell damage. Continuously monitored water bath temperatures of 40° are recommended. Temperatures higher than this will increase cell metabolism such that oxygen demand surpasses oxygen delivery and further cell death will occur. Warming frozen tissue near a fire or in the exhaust of a vehicle will certainly increase the tissue damage. Since it is almost impossible for an expert even to assess the severity or extent of damage at the time of injury,[268] bed rest and careful wound care form the basis of therapy.[179,186,229,241,242,245,246,258-261] Early amputation or wide debridement usually sacrifice too much tissue.[179,242,245,258,259,269,270]

It cannot be stressed too strongly that of all treatment variables a poor outcome is most frequently associated with premature surgical intervention.[242, 258] Even minor surgery must be avoided because tissues are poorly perfused or frankly necrotic and do not heal.[179,242, 258] Sutures, drains, and packing materials only serve as potential sources of infection. Traction is contraindicated. Ointments and greasy medications may lead to tissue maceration. The skin should be kept dry and vesicles left intact. After several days, whirlpool therapy provides gentle debridement. Active range of motion exercises and other physical therapy prevent contractures due to immobilization.[271] Therapies such as hyperbaric oxygen,[272-274] vasodilators,[268] corticosteroids,[268,275,276] and anticoagulants[165,192, 277-279] have been suggested from theoretical considerations, but none has proved beneficial. Sympathectomy before the development of gangrene has been claimed to decrease morbidity.[261,280-282] Although it probably decreases pain, hyperhydrosis, and edema, and leads to more rapid demarcation of nonvital tissue and faster healing of ulcers, sympathectomy probably does not diminish tissue loss.[261,283] Doppler ultrasound and digital plethysmography[284] may identify patients in whom sympathetic blockade will decrease tissue loss.

The problem of amputations in the treatment of cold injury has been discussed extensively. It has been claimed that angiograms[285] and xenon 133 flow rates[203] demonstrate early demarcation of nonvital tissue and that bone scans[311] show nonvital bone, thus allowing for early amputation. Their use has not been widely accepted, however, and in the absence of life-threatening infection or other complications it is probably best to allow tissue to slough of its own accord. ("Frozen in January, amputate in July").[179, 245,258,259,269,270] Bates discusses this subject and recommends specific surgical techniques.[270]

The clinical features of the late stages of cold injury have been summarized.[232,234,286,287] Patients may complain of (in decreasing frequency): cold feet, pain, hyperhydrosis, numbness, abnormal color, and joint stiffness.[286,288] The symptoms are usually worse during cold exposure. Clinical evaluation may show thickening and deformation of nails, alopecia, and atrophy and scarring of skin. Basal cell carcinoma and squamous cell carcinoma have been seen in the skin scars 11 to 34 years following frostbite.[289-292] Histologic

examination may disclose in addition: atrophy and fibrosis of subcutaneous tissue, fat, and muscle, and fibrosis of ligaments.[223,234,241,293,294] Peripheral nerves often display demyelination and fibrosis. Vessel walls are thickened and their lumens may be completely occluded.[295] Bone changes include osteoporosis (seen 4 to 10 weeks following injury and implying viability of bone), juxta-articular punched-out lesions (after 3 to 24 months),[296,297] and arthritis.[298] Acromutilation may be seen in deep injury if tissue loss has exposed bone to air. In children, cold injury to epiphyseal growth centers leads to fragmentation, premature fusion (seen between 12 and 24 months) and later deformity.[299-301]

The treatment of these sequelae can be difficult. As suggested by clinical evaluation,[302] local blood flow is often reduced.[303] This may be due to increased arteriolar tone resulting from permanent damage to peripheral sympathetic fibers. Thus sympathectomy has been useful to alleviate complaints related to sympathetic hyperactivity (hyperhydrosis, cold feet).[226,241,245,246,280-282,304-306] Intraarterial reserpine may be similarly useful.[258,307] However, since angiograms have shown persistent spasm[269] and filling defects even 28 years after cold injury,[248, 300,308] direct damage to vessels also probably contributes to these symptoms. If vasodilators such as phenoxybenzamine, tolazoline, or procaine sympathetic block[306] do not reduce complaints, it is likely that sympathetic activity is not a predominant feature and that sympathectomy will not be beneficial.[246] If peripheral nerve block leads to higher skin temperature (increased circulation), however, it is probable that a sympathectomy will help alleviate the symptoms.[238]

Attempts have been made to define factors that will predict the outcome of cold injury. It seems that amount of clothing, duration of exposure, temperature, and moisture all influence the results. There is a positive linear correlation between tissue loss and the product of ambient temperature and exposure time.[309] In one series,[309] all patients in contact with wet clothes or metal at ambient temperatures less than -7° for more than 1 hour suffered some tissue loss. Specific predictions of amount of tissue loss or line of demarcation were not reliable. Failure of skin to become warm several hours after rewarming, lack of edema or vesicles after 24 hours, hemorrhagic vesicles, fever,

and absence of pulses after 48 hours are all poor prognostic signs. Demonstration of interstitial gas by roentgenography (between 2 and 6 days) suggests eventual tissue loss.[297] Finally, estimations of serum transaminases may indicate outcome. A peak in the first 2 or 3 days usually suggests there will be little permanent damage. Persistent elevations or peaks 10 to 14 days after thawing may indicate ultimate tissue loss.[258]

To summarize, current concepts of the therapy of local cold injury emphasize rapid rewarming, avoidance of refreezing, and intensive medical management.

B. Systemic cold injury

Although reports of persons with hypothermia have appeared sporadically over many years, current interest began in the 1940s when induced hypothermia was used to treat cancer, schizophrenia, opiate addiction, and blood parasites.[312-318] Later it was adopted to facilitate surgery,[319-324] especially cardiac[60,325-334] and neurosurgical[335,336] procedures. It has also been employed in the treatment of intracranial hemorrhage[337] and cardiopulmonary arrest.[338,339] Accidents at sea prompted the study of immersion hypothermia. The report of Prescott[340] to the British Ministry of Health and several letters[341-343] and reviews[344-349] called attention to the problem of hypothermia in the elderly. Pugh[350] and several others[351] emphasize the scope of the problem of hypothermia from accidental environmental exposure. From these observations, an understanding of the physiologic changes during hypothermia has emerged.

The physiologic reaction to hypothermia is diphasic. The changes during induced hypothermia have been summarized.[194,320, 321,352-354] During the initial stages (35° to 30°) there is stimulation of homeostatic mechanisms. As body temperature continues to fall, however, physiologic functions are depressed. Without support, death occurs between 25° to 29°.[355]

The thermal and metabolic responses begin with constriction of small vessels of the periphery (skin,[356] muscle, and nasal mucosa[357,358]), causing blood to be shunted to the core. The skin temperature falls, the rectal temperature rises,[359-370] and the thickness of the effective body insulation increases.[371-373] Differences in organ temperature develop.[374] The

esophageal temperature most closely approximates the blood and brain temperatures.[374,375] (The rectal temperature is usually falsely low.[374,376]) There is no vasoconstriction in the skin of the forehead,[377] except the ear, and at low temperatures heat loss from the head can be high (50% of resting heat output at -4°).[378] Other regions of high heat loss include lateral thorax, upper chest, back, and groin.[379] Sweating may occur as a manifestation of central nervous system stimulation.[380] Shivering begins (wide variation of temperature at onset[359]) and increases heat production.[361,375,381-384] Oxygen consumption rises from four[365] to nine[382] times that of resting levels.[360,364,367,381,383-387] Shivering decreases the effective body insulation.[372] If the heat generated is inadequate to rewarm the body, a rapid fall of core temperature ensues. (There is no good evidence for nonshivering thermogenesis in man.[367,368]) Below 33° shivering is replaced by muscular rigidity. Metabolic processes are slowed, carbon dioxide production decreases,[388] and oxygen requirements fall.[334,335,385,388,389] Estimates of oxygen consumption range between 65% of normal at 26° [335,353] and 4% at 10°.[389]

There are several factors which affect the timing and pattern of response.[390] The colder the environmental temperature, the more rapid is the fall in body temperature.[366,381,391] Wind accelerates heat loss.[363,366,392] Ambient humidity has no effect.[362,363,366] Subcutaneous fat acts as an insulator, and fat persons maintain body temperatures more successfully than thin ones (higher rectal temperature, lower skin temperature, less shivering and oxygen consumption).[48,350,371,393-402] Despite its action as a peripheral vasodilator, alcohol does not accelerate the fall of rectal temperature.[403,404] It may retard the fall of finger temperature, and it seems to help alleviate the misery of cold exposure.[404] Similarly, oxygen administration may increase the sensation of warmth, retard the onset of shivering, decrease oxygen consumption, and reduce the respiratory response to cold,[387] but it does not alter the pattern or rate of fall of temperature.[405] Clothing retards heat loss,[399,406] but both moisture and exercise (because of bellows-like movement) decrease its insulative value.[392,407,408] In cold water, exercise accelerates heat loss (probably by increasing return of cold blood from the extrem-

ities[371,379,386,399,401,409,410] and increasing conductive loss). In cold air[403] and warm (24° to 35°) water[727] vigorous exercise (more than 800 calories/hour) may help maintain body temperature.[408] In addition, the following have been claimed to affect the response to cold: age,[361,411-414] sex,[415] season, time of day, physical condition, previous cold exposure, food consumption, and carbon dioxide administration.

The changes of cardiovascular parameters during hypothermia have been reviewed.[353,388,416,417] Immediately following cold exposure the pulse,[116,364,387,404,406,418-421] blood pressure,[418,421-424] cardiac output,[418,425] and stroke volume[425] increase. (The mean pulse was 146 beats/min and mean blood pressure 158/85 mm Hg in one series.[418] Stroke volume increased by 78%[425] and cardiac output by 60% to 100%.[388,418,425]) There is sustained peripheral venous[422,426] and arteriolar constriction. As core temperature falls, deterioration of cardiovascular function begins. The heart rate decreases linearly with temperature,[365,388,423,424,427-434,755] due to intrinsic slowing of pacemaker activity of the sinus node,[435] slowing of conduction velocity,[436,437] and slowing of myocardial contraction velocity (prolongation of systole).[419,429-431,433,444] The nadir of the pulse usually coincides with the nadir of the rectal temperature.[423] Stroke volume is unchanged.[424] Cardiac output falls (10% to 57% of normal at 30°).[385,424] The central venous pressure increases[423] to as much as 14 cm of water.[422] The circulation time increases.[424,438] At 30° the left ventricular oxygen consumption is 33% of normal.[439] Below 25° myocardial contractility[440] and left ventricular compliance[441] decrease, and left ventricular end diastolic pressure increases.[441] Hypotension develops,[365,442] and the pulse and blood pressure are usually not detectable below 25°.

Reflexes involving aortic baroreceptors, the carotid body, or sympathetic vasoconstrictor fibers are intact but slowed.[423,443]

Several changes in peripheral circulation result in poor perfusion. There is direct constriction of small arteries, arterioles, and small veins by cold. Total peripheral resistance is thus initially elevated[195,424,444] and blood flow to all tissues is reduced. The pattern of distribution of blood flow is altered such

that flow to the brain, heart, and shivering muscles is maintained at higher relative levels.[354,445] As core temperature falls below 30°, peripheral resistance begins to decrease.[195] Transudation of fluid leads to increased concentration of plasma proteins and erythrocytes. This increases the viscosity[195,334] (twice normal at 20° [194]) and yield-shear stress[446] and decreases the suspension stability of the blood. Intravascular aggregation of erythrocytes begins near 32°.[196-198] At lower temperatures, decreased arteriolar pressure,[447] decreased blood flow, and formation of platelet aggregates lead to further erythrocyte aggregation.[198] Below 25°, clumped erythrocytes may block capillary entrances, and between 5° and 15° capillary circulation ceases.

The changes of the electrocardiograms of adults undergoing surgical hypothermia[419,428-434,448] or suffering from accidental hypothermia[420,449,450] or hypothermia due to sepsis[451] have been summarized. With decreasing temperature there is progressive lengthening of intervals, changes in configuration of waves, and disturbances of rhythm. The PR interval is prolonged[419,429,434] as much as 40% (or 0.02 to 0.05 seconds)[431] in 50%[433] to 84%[432] of patients. AV block developed in 24% of one series.[432] The QRS interval is lengthened.[419] Prolongations by 40% to 92%[431-433] were present in 92% of patients in one group, and 54% developed intraventricular conduction delays.[432] The intrinsicoid deflection may be delayed by 29%.[431] The QTc interval is increased[429,430,434] by as much as 44%[431] (or 0.01 to 0.27 seconds[419,433]) and can remain prolonged even after the temperature has returned to normal.[420,448] The ST interval was increased in 30% to 70% of patients.[432]

The QRS complex may increase in amplitude between 35° and 30°, but its axis remains unchanged. Below 35° there is progressive elevation of the J point, leading to "Osborne waves." They are oriented anteriorly and to the left[420,434] and thus are most prominent in V4 and the left ventricular limb leads.[452] In other leads the QRS complex is lengthened without forming a distinct wave. Bundle-branch block can mask Osborne waves.[452] With decreasing temperature, they may disappear or become higher and broader.[429,434,453,454] When they are very high, the T wave may flatten or invert.[429,434] The cause of Osborne waves is unknown. They are

probably not due to myocardial anoxia, injury, acidosis, or atrial repolarization.[434] They may result from altered ion flux across sarcolemmal membranes.[454] Osborne waves are relatively specific for hypothermia, but they have been seen at normal temperature[455] and with subarachnoid hemorrhage.[456]

ST segments may be elevated or depressed by 0.5 mV, and elevations of 0.5 mV have been seen during rewarming.[448] Emslie-Smith has studied vectorcardiograms and claims that with hypothermia the angle between the QRS and T loops is increased[457] and that the duration of the J loop correlates with the degree of hypothermia.[454] Alterations in T-wave configuration, amplitude (0.2 mV change), and axis may occur independent of J point changes.[433,458] They may be due to epicardial hypothermia.[459,460] T-wave inversion occurs rarely.

The most common arrythmia is sinus bradycardia. Below 30° the PR interval lengthens and AV block may develop. Atrial fibrillation begins in the range of 22.5° to 32.0° (means of 27.2°,[431,433] 28.9°,[434] and 31.6° [432] for four series) but can be seen at higher temperatures in older patients.[430] Recordings of the His bundle have shown prolonged AV intervals[436,437] (not shortened by atropine[436]) and normal HV,[436] PA, HQ and HS intervals.[437] These imply a conduction defect in the AV node. Atrial tachycardia, atrial flutter, and wandering atrial pacemaker have also been seen. Ventricular fibrillation can be seen in the range of 23.8° to 27.8° and its onset is usually preceded by premature ventricular contractions or a delay of the intrinsicoid deflection of 24% or more.[431] The cause of the increased frequency of ventricular fibrillation is not known. It may be caused by circus movements resulting from lengthening of conduction time without a proportional increase in refractory period.[461] Slowed conduction leading to uncoordinated myocardial contraction has been suggested.[462,463] Finally, intramyocardial temperature gradients may play a role.[464,465] With further cooling, the ventricular waves become smaller until asystole punctuated by irregular ventricular complexes develops (between 10.5° [419] and 20° [428]).

In infants, normal sinus rhythm is present to 18° to 20°. The PR, QRS, and QTc intervals are lengthened. No alterations in waves are seen.[427,435]

Surgical manipulation may give rise to a nodal rhythm or premature ventricular beats.

During the initial stages of hypothermia, the respiratory rate,[387,466] tidal volume,[466] minute volume,[360,381,383, 387,431,466] and alvolar ventilation[406,467] are increased. The peak increase of respiratory rate was 14.8 to 15.7 breaths/min, the peak of tidal volume was 0.68 to 0.79 liters, and the peak of minute volume was 9.8 to 11.1 liters/min in one series.[466] As body temperature falls to less than 30°, however, respiratory rate and tidal volume fall. Accumulation of blood displaced by peripheral vasoconstriction may cause pulmonary congestion[468] and decreased vital capacity.[469] Airways resistance may increase,[466] but compliance is probably unchanged[388, 466,470] above 29°. Carbon dioxide excretion is not impaired,[388,471] and oxygen uptake remains normal.[472] Breathing cold air by normothermic persons increases airways resistance;[473] decreases maximum breathing capacity;[473] but does not change FEV_1,[473-476] maximum expiratory flow rate,[473,475] FVC,[475] or nitrogen elimination.[475]

With decreasing temperature, the solubility of gases increases, the protein anion buffer concentration decreases, and the pKa of carbonic acid increases.[477] The result of these trends is that the pH[478] and bicarbonate concentrations rise and the pCO_2 and pO_2 fall.[479,480]

The glomerular filtration rate drops to 52% to 67% of normal, and the renal plasma flow to 56% to 59% of normal, probably due to vasoconstriction.[442,481] (Renal vascular resistance is increased.[481]) Shivering may reverse these changes.[482] Urine flow increases[147,364,483,485,575] and may range between 1.4[442] and 3.9[486] ml/min above basal. Plasma volume shrinks[444,487-489] (6% to 12%[424]) and the total protein concentration of the plasma rises,[484] (0.5 gm/dl[490]). This diuresis is inhibited by exercise, upright posture,[364] and small doses of antidiuretic hormone.[486,490] It is probably due to decreased antidiuretic hormone release because of central venous congestion and decreased tubular resorption of water. Similarly, altered tubular metabolism leads to increased sodium,[147,481,484] chloride,[484,486,490] and magnesium excretion, even in the absence of diuresis.[485] Potassium excretion is increased,[147] normal,[481,484,485] or reduced.[442] In dogs, bicarbonate

[491] and glucose[492] reabsorption is reduced. Thus, the urine comes to resemble an ultrafiltrate of plasma, and urine/plasma ratios of electrolytes and creatinine approach unity.[486,493]

Serum electrolytes are maintained at normal levels during moderate hypothermia. Below 25° the potassium concentration may decrease[319,442,481,494,495] or increase.[496] Serum calcium may increase or decrease.[319,494] Its binding to albumin is unchanged.[497] Two studies report low serum sodium levels.[319,481] No changes in chloride or magnesium have been reported in humans.

Uncomplicated hypothermia probably does not cause alterations in acid-base status.[498] Related changes such as volume depletion or poor peripheral perfusion and underlying disorders such as pneumonia or keto-acidosis may, however, cause alterations of pH and blood gases.[499]

Dysarthria, drowsiness, inattentiveness, and impaired recent memory develop between 30° and 34°.[500] Cold slows nerve transmission (1.4 m/sec/deg).[501] Pupillary reaction to light, superficial abdominal reflexes, and deep tendon reflexes are present above 30°, but at temperatures less than 25° all reflexes are absent.[502] Cerebral vascular resistance rises and cerebral blood flow falls.[444,503] At 30° it is 60% of normal. Cerebral oxygen consumption falls,[503] and at 28° it is 25% to 40% of normal.[444] Extrapolation from these values suggests that the adult brain should tolerate 10 minutes of complete circulatory arrest at 30° and 50 minutes at 10°.[319,389] The infant may tolerate 50 minutes of arrest at 22° and 60 minutes at 20°.[325] Complete recovery by an adult after 14.5 minutes of complete circulatory arrest at 24° has been reported.[335] With decreasing temperature, electroencephalograph voltage falls to less than 50 mV.[504] EEG recordings during mild hypothermia had diffuse, sharp, diphasic and triphasic discharges (to 300 mV at 1/sec) synchronously in all channels.[505] Below 20° the EEG is silent. Following rewarming from temperatures of 30° to 32°, patients have demonstrated drowsiness, elevated spinal fluid pressure, elevated spinal fluid protein[500] or choreoathetosis.[506,507] Following rewarming from temperatures less than 24°, most patients show neurologic findings ranging from transient confusion to hypotonia of postural muscles to

coma.[508] At temperatures below 12°, patients have developed focal cerebral necrosis, probably due to intravascular platelet and erythrocyte plugs.[509]

Long-term studies suggest that following surgical hypothermia infants may experience developmental delay or psychomotor disorders.[507,510] Results of IQ testing have been normal, however.[511,512]

Psychomotor testing during experimental cold exposure shows a decrease in tracking proficiency.[214,513] Reaction time to visual stimuli has not changed at temperatures above 35°, [213,214,514] although reaction speed probably is increased in high windchill situations.[514]

The thyroid response to cold is controversial. Neonates and infants increase TSH in response to cold.[515,516] Some have reported elevated TSH and decreased PBI levels after 2 hours in the cold,[517] elevated T3 and T4 levels after 2 to 4 days of cold exposure,[518,519] and elevated T3 during the winter.[520] Others have found no change in PBI,[484,487,552] TSH,[487,520-523] T_4,[520] T3 resin uptake,[484,487] or thyroid binding globulin[487] during experimental hypothermia. In persons with accidental hypothermia, TSH,[524,525] free T_4,[524] and PBI[349,526,527] have been normal. Their response to TRF is normal.[524]

With cold exposure, there is release of epinephrine and norepinephrine.[147,483,484,487,528]

In experimental cold stress, serum cortisol levels have been normal[517,518,520] or elevated.[484,487,519] Urine 17-hydroxysteroids[529] have been normal and 17-ketosteroids have been decreased[484] and elevated.[147,530] The adrenal response to stress may be blunted.[531,532] In some patients with accidental hypothermia, serum cortisol is normal[524] or elevated[525] and plasma 11-hydroxycorticosteroids[526,527,533,534] and urine[535] or serum 17-hydroxycorticosteroids[536] are high. The half-life of cortisol is prolonged.[526]

Although insulin levels during surgical hypothermia may be above reference ranges,[537,538] the levels are below those appropriate for concomitant serum glucose levels in patients with normal temperatures.[537,538] This implies impaired islet cell function.

Growth hormone levels during experimental cold exposure have been unchanged.[517,521,539] Its relationship to glucose has been disturbed in patients with accidental hypothermia.[524,525]

Cellular metabolism is impaired. Glucose levels may be high[540] because of low insulin,[494] high cotisol, and diminished cellular uptake.[435,541] Fructose metabolism may also be impaired.[542] Elevated catecholamines lead to mobilization of fat and serum glycerol,[435,488] and triglyceride levels are high.[488] Serum free fatty acids are unchanged[435,488] or elevated.[527,543,544] Serum lactate may be elevated if there is poor delivery of oxygen to peripheral tissue.[435,540] (In dogs, hypothermia reduces hepatic metabolism of lactate.[479,545])

Hematologic changes include a decrease in plasma volume[444,487,488] (6% to 12% at 30° [424]) due to diuresis, sequestration, and fluid shifts. Thus the hematocrit[364,442,444,484,487,490,546] and erythrocyte counts rise.[424] Above 30° the leucocyte count is normal or elevated (with a left shift, decreased eosinophils, and decreased lymphocytes). With further hypothermia leucocyte counts fall, possibly because of splenic and hepatic sequestration or margination. Platelet counts may be low[319,334] or normal.[547] Platelet aggregation is sluggish,[548] and bleeding time may be prolonged.[474,549] In neonates with hypothermia the thrombin time is prolonged (possibly a result of disseminated intravascular coagulation[550]) and platelet counts may be low.[551] Other coagulation studies (venous clotting time, prothrombin time, and thrombin generation time[547,552]) and levels of clotting factors (I,II,V and VII)[547] are normal at moderate hypothermia (30o). At 20° the venous clotting time is doubled.[334] Cryofibrinogen levels may be elevated.[553]

In newborns, hypothermia may cause subcubtaneous fat necrosis[553,554] with later calcification.[555,556] This is thought to be due to less oleic acid (freezing point -10.3o) and more palmitic acid (freezing point 17.1o) in neonatal fat.[555,557] With decreasing temperature the fat solidifies and disrupts cells. After thawing, the free fat provokes an inflammatory response, leading to fat necrosis, calcification, and fibrosis.

Studies of gastrointestinal function in humans have not been reported. In experimental animals, gastrointestinal motility is decreased[558] and ceases at 30°. Bile production slows,[559] but the concentration of cholic acid remains unchanged.[560] Bile flow ceases at 23°.[561] At similar temperatures, pancrea-

tic secretion slows and the concentration of digestive enzymes in pancreatic juice and serum drops.[562]

The function of the immune system during hypothermia has not been studied in humans. Hypothermia has increased susceptibility to pneumococcal sepsis in the rabbit[563] and decreased susceptibility to pneumococcal peritonitis in the mouse.[564]

The effects of hypothermia on the fetus have not been studied. In a series of dogs subjected to hypothermia, five were pregnant. Of these, two suffered spontaneous abortions within two days of rewarming.[565]

The clinical features of accidental hypothermia have been presented in several case reports[370,358,566-577] and general discussions.[575-584] Other reports discuss general physiologic,[585-588] cardiovascular,[416,589] cardiographic,[420,449,450,452,453,458] respiratory,[489-592] renal,[593] acid base,[567,589,590,592,593] metabolic,[416,527,535,593] neurologic,[593] endocrine,[349,535] and hematologic[589,593,594] aspects of persons with accidental hypothermia.

Several disorders may predispose to or even cause hypothermia.[340,586,595-597] Hypothyroidism (and thus panhypopituitarism and adrenal insufficiency) leads to inadequate heat production, and most patients with severe myxedema will have low body temperatures.[598] The diagnosis of hypothermia is difficult because euthyroid patients with hypothermia may show many of the signs of myxedema.[599] Prolongation of the contraction/relaxation ratio of the ankle jerk reflex[600] and a serum cholesterol concentration greater than 350 mg/dl[599] are said to be signs of hypothyroidism in a hypothermic patient. Protein-calorie malnutrition (as in starvation,[535,601,602] celiac sprue,[603] or anorexia nervosa[604]) leads to decreased calorigenesis. In hypoglycemia of any cause, function of the central nervous system thermoregulatory centers is disturbed because of low cerebrospinal fluid glucose concentration.[535,605-609] Structural alterations in the anterior hypothalamus[610,611] (tumor, stroke, trauma, gliosis, Wernicke's encephalopathy,[566,612,613] Shapiro's syndrome[614,615]) can similarly disrupt these centers. In patients with spontaneous periodic hypothermia, there are no anatomic findings; this syndrome may be a manifestation of an autonomic seizure disorder.[616] In patients with cervical spinal cord transections, the sympathetic fibers controlling

vessel tone and shivering are interrupted, leading to susceptibility to hypothermia.[617] Extensive burns, erythroderma, and exfoliative dermatitis[618-620] also prevent cutaneous vascoconstriction and increase transepidermal water loss,[621] leading to increased heat loss and hypothermia. Barbiturates[622-626] (especially short-acting barbiturates[627]), ethanol, diazepam,[628] phenothiazines,[349] tricyclics,[535] and general anesthetics predispose to hypothermia through interference with central nervous system regulation. The use of phenothiazines in patients with myxedema is especially dangerous.[629-632] Finally, some persons suffer chronic hypothermia with no demonstrable cause.[633]

One of the most important features to stress is that profound hypothermia may be difficult to distinguish from death.[567,587,634,635] The patient is comatose. The skin is cold and the tissues are stiff. The respiratory rate and tidal volume are low. Peripheral pulses are not usually palpable, and cardiac sounds are difficult to hear. Blood pressure is often unobtainable. Slowed nerve conduction prevents deep tendon reflexes and pupillary reactions. The EEG may show no activity below 20°. Despite these findings, however, full recovery is possible.[636,637] Thus, the diagnosis of death under field conditions is usually not warranted. Perhaps the best approach is to use failure to revive following rewarming as the only secure criterion of death from hypothermia.

The therapy of accidental hypothermia has been reviewed.[388,586,635,638-642,725] Although therapy is tailored to the clinical setting, rewarming the patient forms the basis,[571,634,635,643-656] and rapid rewarming increases survival.[587,635,643,649,654]

There are several rewarming techniques and they can be grouped into passive (blankets, removal from the cold environment), active external (immersion in hot water, electric blankets), and active core (inhalation of heated gases, dialysis). For most patients with a temperature greater than 32°, one of the passive or active external techniques is usually adequate. In alert, young, otherwise healthy patients or those suffering from hypothermia due to rapid heat loss, these techniques may be adequate for temperatures even 1 or 2 degrees lower. Children, because of larger surface area-to-weight ratio, can be rewarmed from lower temperatures by external techniques.[657]

For persons who have core temperatures less than 32°, who have been hypothermic for more than 8 to 12 hours,[649] or who have limited cardiovascular reserve, core rewarming is probably safer.[649-651]

Techniques such as extracorporeal blood warming [571,650,652,653,728] and thoracotomy with pleural lavage[729] have been used, but they are not practical for most situations. The use of heated inspired gases has also been advocated.[570,646,647,658,659] Theoretical calculations, however, show that this method transfers very little heat.[660] Clinical trials have found it no more effective than immersion in hot water.[648,661] It is the only technique for active core warming for which portable equipment is available, however.[658,659,662] Rapid peritoneal dialysis has also been used.[622,634,649,663] The technique is easy and can be used even in first aid centers. It provides the ability to manipulate glucose and electrolyte levels and extract unwanted drugs.

Regardless of technique, the patient should be rewarmed until sweating occurs. This usually results in some overwarming. If rewarming is stopped, however, when the patient subjectively feels warm (usually as shivering ceases) only half the heat debt will have been recovered.[369] Core temperature is most easily monitored as rectal temperature, although tympanic membrane temperature may accurately reflect deep organ temperature.[664-666]

Several problems are seen frequently in persons with hypothermia. The chilled myocardium is said to be irritable, and arrythmias are common. Ventricular fibrillation is seen below 28° and may account for the mechanism of death in most persons. At low temperatures neither DC countershock nor drugs commonly restore sinus rhythm. Instead, cardiac massage should be instituted and the patient warmed to 30°.[634] Spontaneous conversion may then occur, and failing that, DC countershock is often successful.[571] Intravenous magnesium sulfate may facilitate cardioversion.[667] Bretylium tosylate may prevent ventricular fibrillation and may facilitate cardioversion.[752]

Although most authors agree that blood gas determinations must be corrected for low temperature, some argue that for practical purposes pH and pCO_2 measurements need not be corrected.[591,669,670] For pO_2 levels, on the other hand, corrections must be made by means of a nomogram.[480,671] The more funda-

mental problem, though, is that normative values for blood gas determinations during hypothermia have not been established; thus the consequences of alterations of blood gases is unclear. There is some evidence, however, that during surgical hypothermia, sinus rhythm is restored spontaneously more frequently if the pH is maintained below 7.30 (at the patient's temperature) and pCO_2 at 40 mm Hg (at the patient's temperature) during the time the patient's temperature is below 30°.[672-675]

During rewarming, the core temperature almost always drops initially.[369,401,421,661] As circulation is reestablished in the peripheral tissue, cold blood is returned to the core, and core heat is lost warming the cold periphery. Thus core temperature can fall as much as 3 to 5 degrees.[635,676] During this time, shock can also develop. The reduced blood volume is inadequate to maintain circulation through peripheral tissue. The likelihood of shock is minimized if rewarming fluids are less than 40°.[652]

Many persons with accidental hypothermia have elevated glucose levels, often with dilutional hyponatremia.[541] Cellular metabolism of glucose is probably depressed. Sluggish islet cell function also contributes to hyperglycemia. (Normal and slightly elevated levels of insulin have been seen following accidental hypothermia;[524] however, insulin levels are below those appropriate for concomitant serum glucose levels in persons with normal temperatures.) In addition, peripheral tissues are probably refractory to insulin action.[435,541] Thus doses of insulin required to correct the hyperglycemia may cause profound hypoglycemia as the patient is warmed. For this reason hyperglycemia should be treated conservatively.

Although uncomplicated hypothermia does not lead to alterations in acid-base balance, associated volume depletion, circulatory changes, and underlying disorders may complicate the situation. Metabolic acidosis is often present[535] and may be treated with cautious use of bicarbonate.[644] Analagous to the situation with hyperglycemia, post-rewarming alkalosis may result if the acidosis is too vigorously treated. Serum potassium is often high, but it may be low[535,638] as well. Total body potassium is usually low and potassium supplements may become necessary. Hypophosphatemia may develop.[677]

Other general supportive measures are usually necessary. The heart should be monitored continuously. Changes in the electrocardiogram may persist several hours after rewarming, and widening of the QRS complex and prolongation of the QTc interval are usually the last aberrations to improve. Congestive cardiac failure may develop.[678] Intravenous fluids are usually required, and in cases of slowly developing hypothermia, severe volume depletion may be present. A central intravenous catheter may facilitate decisions regarding fluids; but with cold related myocardial irritability, care should be taken to avoid its entrance into the heart. Oxygen by mask or endotracheal tube may be required.[643,644,678,679] Careful attention to bronchopulmonary toilet is needed because of increased bronchial secretions.

If myxedema is a consideration, levothyroxine and hydrocortisone should be given. Otherwise, corticosteroids probably have no use.[526] In experimental animals, low-molecular-weight dextran decreases capillary sludging[680,681,724] and may lead to improved chances of survival.[682] Its use in humans has not been studied. In general the pharmacokinetics of most drugs at low temperatures have not been established.[723] Some antibiotics are less effective.[564,683] Halothane solubility in blood is increased.[684] Nondepolarizing neuromuscular blocking agents are more active.[685] Because of these variations from normothermic kinetics, most drugs should be avoided.

Commonly associated conditions include myocardial infarct, stroke, pneumonia, sepsis, diabetes mellitus, and uremia.[341,349,536,576,585,592,686-689]

Subsequent complications include pancreatitis[317,594,690-692] and disseminated intravascular coagulation.[594] Anemia may develop, possibly secondary to direct effects of cold on the bone marrow or damage to erythrocytes during cold-induced aggregation.[198] During the 4 days following rewarming from 30° or 31°, some patients showed drowsiness, elevated spinal fluid pressures, and elevated levels of spinal fluid protein.[500] Emotional lability, memory loss, hypotonia, and other neurologic findings have been seen several days following severe hypothermia and may result from capillary sludging and microinfarction.[508,509] Acute and chronic renal failure have occurred.[693] Elevated serum enzymes (total CK,CK1,[694]AST,and ALT)

may indicate damage to liver, myocardium, or skeletal muscle.[695,696]

The mortality from accidental hypothermia averages about 40%, but may be as high as 100% in patients with rectal temperatures less than 28°.[342,346,348,585,596,689,697,698] Although the nadir of body temperature is important in determining outcome, especially in patients with myxedema coma,[699] the nature and severity of the underlying disease may be the most important factors.[698] Some claim that elevated levels of cryofibrinogen[553] or serum 11-hydroxycorticosteroids[534] indicate a poor prognosis. Autopsies on patients dying from hypothermia have not shown specific lesions. Gastric mucosal hemorrhages and pancreatitis are often seen.[293,314,317,535,585,686,689,700,701]

In summary, the clinical approach includes diagnosis and correction of disorders (primarily endocrine and neurologic) that can predispose to hypothermia. Treatment of hypothermia emphasizes rewarming and careful monitoring and support of cardiovascular, pulmonary, and metabolic functions.

C. Immersion hypothermia

Because of the many accidents at sea, the problem of hypothermia from cold water immersion has received special attention.[702-704] The higher thermal conductivity of water and other factors increase the heat loss in water to twice that in still air at the same temperature or approximately that of air at 5 miles/hour.[386] At water temperatures above 27° body temperature falls slowly for approximately 1 hour, at which time heat production from shivering balances heat loss. If the water is colder, rectal temperature falls faster and to a lower level.[386] One hour's exposure to water at 4° will be fatal for 50% of persons,[355] and almost all will die after two hours at the same temperature. Similarly, most persons will survive if the nadir of rectal temperature is 33°, 50% will survive a nadir of 31°, and very few will survive if the rectal temperature is below 24°. The factors listed previously have influences in specific cases, and variation from these figures has been seen. Several formulas and nomograms attempt to integrate these factors to predict survival times or tolerances to cold.[386,407,705-707]

D. Dermatologic disorders

Dry skin is a common problem that sometimes leads to fissuring, bleeding, and loss of function. Skin biopsies have shown epidermal thickening of exposed areas.[708] Many have noticed brittleness and easy fracturing of the fingernails and toenails.

E. Ophthalmic disorders

A unique type of corneal opacity known as "Labrador keratopathy" has been described.[709] It begins as minute droplets of unknown material in the cornea at the medial and lateral limits of the interpalpebral fissure. The pupillary area may become involved, causing decreased visual acuity. In the late stage, large yellow corneal nodules are evident. The etiology is unknown.

Snow blindness (ultraviolet keratitis) is a danger. Prolonged exposure of the conjunctiva to ultraviolet irradiation under any circumstances causes damage. With the many reflecting surfaces of snow and ice, damaging exposure can occur in several hours on a sunny day. Because ultraviolet irradiation is filtered by the atmosphere, at high latitudes the risk becomes less. Treatment is the same as that prescribed in temperate zones.

F. Optical disorders

Work in the cold causes problems for those wearing spectacles. Plastic can become brittle and can break easily. Stresses due to rapid change of temperature can in themselves cause breaks. Grant has catalogued the sites of breakages of frames.[710] Metal frames can cause cold injury if they touch the skin and should therefore not be used without covering. Contact lenses may offer the fewest problems during outdoor work. With low humidity, however, the cornea is more vulnerable, and the lenses may not be well tolerated.

G. Dental disorders

The high frequency of dental complaints has been recorded by many.[711] For example, in 1956-1957, 97% of men at one Antarctic base sought dental treatment, most commonly for cold induced odontalgia and pain from

hypersensitive cervical dentin.[712] Early explorers related tooth fracturing and loosening of amalgam restorations because of the cold.[712,713] Although the teeth cool significantly during cold exposure[714] (the anterior maxillary teeth may be as cold as 1.7°C after one hour at -2°C ambient temperature[715]), tooth fracturing is rare unless the stress of rapid changes in tooth temperature is coupled with physical trauma to the tooth.[712,713,716] Loss of restorations is usually due to decay, undermined enamel, or trauma.[712] Because tooth sensitivity due to conduction of cold through restorations can be a problem,[716] restorations should have insulated bases. Cold retards bacterial multiplication[715,717] and stimulates saliva flow[718] and these effects may explain the lower number of lactobacilli in saliva[719] and the lower rate of caries[713] seen in outdoor workers. Despite the protective effects of cold exposure, though, there is higher incidence of caries in the Antarctic. This is probably due to poor oral hygiene, frequent eating, and soft food (lacking in mechanical cleaning action[717]). An increased incidence of alveolar osteitis has been noted.[712]

H. Miscellaneous

Epidemiologic evidence suggests that with decreasing temperature there is an increasing risk for myocardial infarct[720] and a decreasing risk for toxemia of pregnancy.[721]

In summary, polar life leads to both adaptive and pathologic conditions. We have tried to collate biomedical information pertinent to these changes. We hope this summary will serve both as a resource and a stimulus for those living and working at the poles.

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