Chapter 15

NONFREEZING COLD INJURY

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INTRODUCTION

Nonfreezing cold injury (NFCI), a syndrome (formerly known as trenchfoot, pernio, and other names) resulting from damage to peripheral tissues in the extremities exposed to cold temperatures,[1–3] remains a major threat to individual military personnel and to military operations carried out in cold weather. NFCI is an injury that does not involve freezing of tissues, which normally distinguishes it clinically and pathologically from freezing injuries,[1] although it is not uncommon for freezing and nonfreezing forms to coexist in the same individual or limb. Whenever military forces are required to operate in cold, wet conditions for more than a few hours, it is always possible that those operations and the health and well-being of personnel will be severely jeopardized or curtailed by NFCI.

The clinical syndrome of NFCI has been known for centuries; however, it is primarily within the military context that it has engendered sustained clinical and historical interest. Observations of NFCI in the military, from earlier times to the present, have been detailed in well-documented historical reviews.[3–5] There has been little continuity in the research efforts to better understand the pathophysiology of NFCI because episodes of interest in the prevention and treatment of NFCI have usually followed periods of major military operations in inclement weather conditions but then unfortunately have been abandoned until the cycle is repeated in further military operations (Exhibit 15-1).

Cold injury is believed to be far more prevalent in combat environments than noncombat or civilian situations under similar conditions of exposure to cold weather.[4,6,7] Because NFCI has been infrequently reported in civilian personnel, it has until recently remained rather obscure as a medical problem. It often goes unrecognized during assessment of individuals suffering from the consequences of cold exposure, as it does not attract emphasis in traditional training about cold-weather medicine. NFCI has received some attention in the civilian sector, however, as a problem related to cold weather medicine in areas such as the homeless,[8] alcoholics,[9] the elderly,[10] and outdoor winter activities.

At present the only if often unattainable strategy for control of NFCI is prevention. As this is frequently not an option, the injury remains a threat to individual military personnel carrying out missions in cold weather. Because NFCI is likely to continue as a substantial medical problem in any extended military cold weather operation, it is currently as important as it ever has been historically to develop effective preventive, diagnostic, and treatment methodologies.

CLINICAL FEATURES OF NONFREEZING COLD INJURY

To further define the syndrome of NFCI, the clinical features will be described (Figures 15-1 through 15-7) before addressing more general considerations of the etiology of the pathology, the treatment, and the prevention of the condition.

The evolution of NFCI in humans, as revealed by clinical studies, involves quite distinctive stages.[1,11–15] Generally, the clinical literature distinguishes four stages, including during and after exposure, and during and after hyperemia, in the progression of the condition; the stages are commonly attributed to Ungley and colleagues.[11,12] The signs and symptoms of different stages are not always clearly demarcated and often blend from one to the next. The time course of each stage is highly variable and some are often short-lived. The presentation and differentiation of the various NFCI stages depend, in a complex fashion, on both the exposure (its duration and the severity of the cold) and on the condition of the individual.

First Stage: During Cold Exposure

The initial stage of NFCI occurs during the period of exposure to the cold environment. Cold exposures that promote NFCI have been reported to vary from just below freezing to 20°C, although the instigation of NFCI may occur at even higher temperatures. Depending on the specific environmental circumstances, exposure durations of less than 1 hour have been reported to induce injury, while exposures as long as a week have been recorded[3] under less severely cold conditions.

The single most important diagnostic criterion is the loss of a sensory modality, most typically complete local anesthesia, which is distinct from premonitory feelings of extreme cold in the affected periphery, almost invariably in the foot although hands can also be affected. Consequently, the most common symptom expressed is that of numbness, although some patients give characteristic descriptions of feeling as if their feet were made of cotton wool, or that they were "wearing someone else's feet," indicating loss of proprioception. As a consequence of these sensory disturbances, casualties may also report disturbance of gait, clumsiness, and stumbling. The extremities may initially be a bright red color, but later almost universally change to a paler color, even completely

EXHIBIT 15-1

THE FALKLANDS WAR: STIMULUS FOR NONFREEZING COLD INJURY RESEARCH IN THE UNITED KINGDOM

It was quickly apparent during the Falklands War in 1982 that a substantial number of casualties with nonfreezing cold injury (NFCI) would be returning to the United Kingdom. Because a high proportion of those were to be Royal Marines, who had a commitment to the protection of the North Atlantic Treaty Organization (NATO) northern flank, and thus would normally be deploying to Arctic Norway within a few months, it was apparent that there could have been a problem. The existing team in the Department of Survival and Thermal Medicine, at the Institute of Naval Medicine (INM), already had great interest and some clinical experience in cold injury. Led by then-Surgeon Commander FStC Golden, Royal Navy, already a leading authority on hypothermia, they quickly assembled the equipment needed to follow up patients with NFCI so that they could advise the command on the future care and disposal of patients.

Guided by the results of questionnaire surveys of returning Royal Marines and Army personnel and both existing literature and outside advice, they knew that they would need to make objective assessments of peripheral nerve and neurovascular function. At first, they employed three techniques:

1. conventional neurophysiological measurements including conduction velocity,
2. noninvasive measurements of peripheral blood flow such as strain gauge, and
3. infrared photoplethysmography and infrared thermography.

A variety of cold stress tests were evaluated, including cold water sprays and forced air convection, to try to elicit evidence of prolonged vasoconstriction following cold exposure. Although the other techniques continued in use until 1985, it was clear that infrared thermography yielded as good information as any, and this later evolved into the standard cold stress test with concurrent thermography still used for clinical assessments today.

Although never reported in full in the open literature, Golden's work demonstrated a number of key features of the mild NFCI that plagued British servicemen in the Falklands. Most important among these was the severity and persistence of cold sensitization following even the most minor cases of NFCI: many of their patients had not reported sick during the conflict but had managed to cope with their symptoms while still fighting. However, on their return to the United Kingdom, most were markedly cold sensitized and few deployed to Norway for the winter warfare training of 1982/83. Golden's work established the INM Cold Injuries Clinic, which today sees about 150 cases each year, drawn from the service and civilian populations in the United Kingdom. It has also reviewed veterans of the Chosin Reservoir campaign (November–December 1950) during the Korean War, who continued to suffer the sequelae of their predominantly freezing cold injuries.

Research at INM has continued in the hands of Oakley, a pupil of Golden's. The former introduced in 1987 the use of thermal sensory threshold measurements to augment thermography, following this serendipitous introduction to the technique by Fowler, one of its developers. In 1991, Golden and Oakley were advised to introduce laser Doppler systems to measure skin blood flow in the peripheries, which Oakley then used for his PhD research at INM between 1992 and 1996. Although laser Doppler techniques can provide intimate detail of the responses of injured microvascular beds to a range of physiological maneuvers, they have not supplanted thermography in clinical assessment. In 1995, Oakley became one of the first investigators to use single capillary laser Doppler velocimetry in his quest for better understanding of the processes promoting cold sensitization. Perhaps most remarkable of all is that the Royal Marines and INM have continued to support a small research program for 18 years; had programs of similar durations been maintained in the past, it is likely that NFCI would be much better understood today.

blanched white. This pallor reflects intense ischemic vasoconstriction in the extremities, which is one of the key features in the pathogenesis of NFCI. Pain and swelling are properly absent at this time, although attempts at rewarming during routine foot care may introduce these third-stage features here at the first stage, and thus complicate the clinical picture.

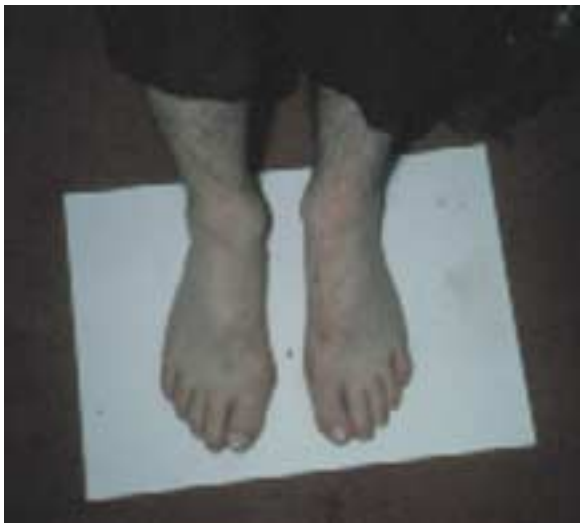

Fig. 15-1. Ungley stage two nonfreezing cold injury in a trainee British Royal Marine. At the time this photograph was made, the feet were still mostly numb and very cold to the touch, but were starting to swell and had changed from white to mottled blue-white. © British Crown Copyright/MOD. Reproduced with the permission of Her Britannic Majesty's Stationery Office.

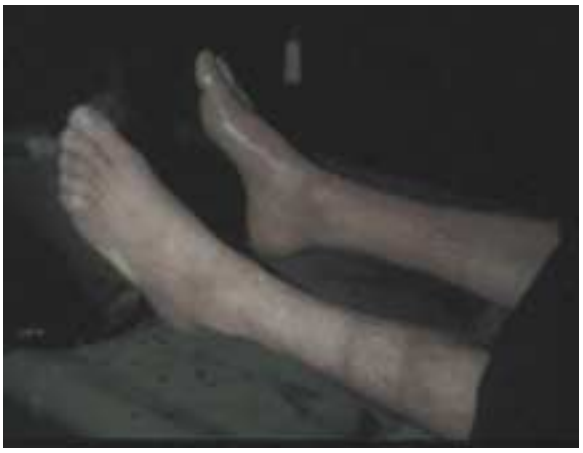

Fig. 15-2. Severe nonfreezing cold injury from the Falkland War. This casualty was recovered from among corpses in the Argentine defensive trenches around Darwin and Goose Green, 3 days after suffering a gunshot wound. The feet (and hands) were very cold, swollen, discolored, and apparently sweaty. Demarcated white patches suggested that some areas had suffered freezing injury. The casualty was also deeply hypothermic (estimated rectal temperature at time of photograph: 28°C). After repatriation, the patient underwent bilateral below-knee amputation. © British Crown Copyright/MOD. Reproduced with the permission of Her Britannic Majesty's Stationery Office.

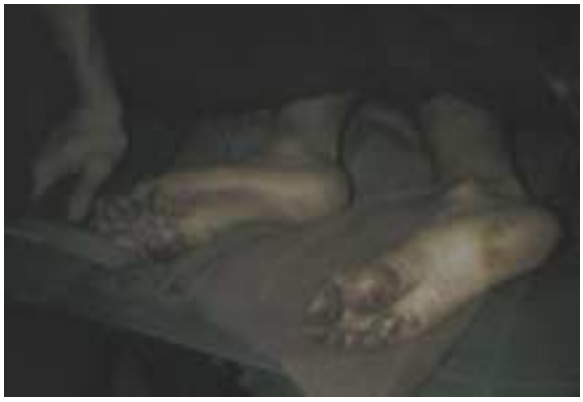

Fig. 15-3. Severe nonfreezing cold injury from the Falkland War. This Argentine soldier had tissue damage in the pulps of the toes and fleshy prominences of the soles of the feet. These appearances are common in those who have been unable to care for their feet for many weeks. © British Crown Copyright/MOD. Reproduced with the permission of Her Britannic Majesty's Stationery Office.

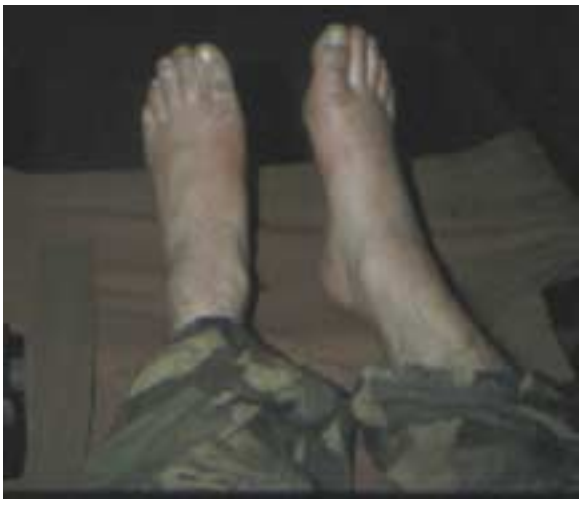

Fig. 15-4. Less severe nonfreezing cold injury in a British infantry soldier from the Falkland War. The feet were swollen, red, and the site of persistent pain. © British Crown Copyright/MOD. Reproduced with the permission of Her Britannic Majesty's Stationery Office.

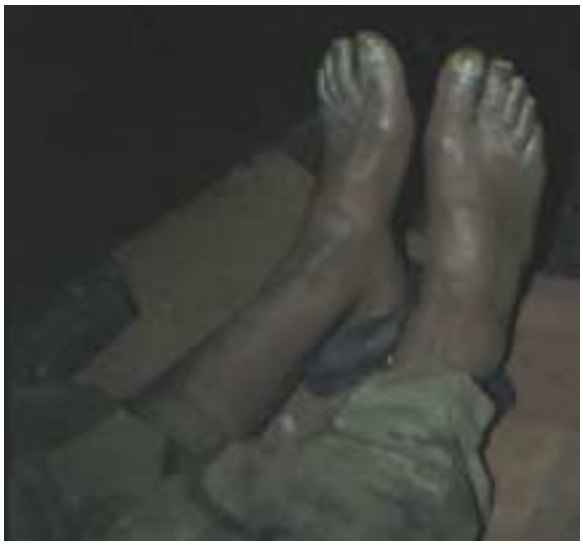

Fig. 15-5. Ungley stage three nonfreezing cold injury in a British infantry soldier with pigmented skin from the Falkland War. The casualty is of African-Caribbean origin, and the characteristic redness of stage three was absent, although the feet were swollen and painful.

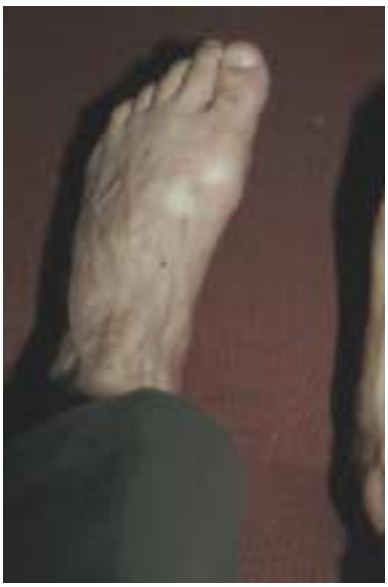

Fig. 15-7. Slow capillary refill demonstrated in mild nonfreezing cold injury. The examiner's two fingers rested gently on the skin of the dorsum of the foot for 10–20 seconds, sufficient to blanch the capillaries. When the pressure was removed, the blanched patches disappeared very slowly, reflecting capillary stasis.

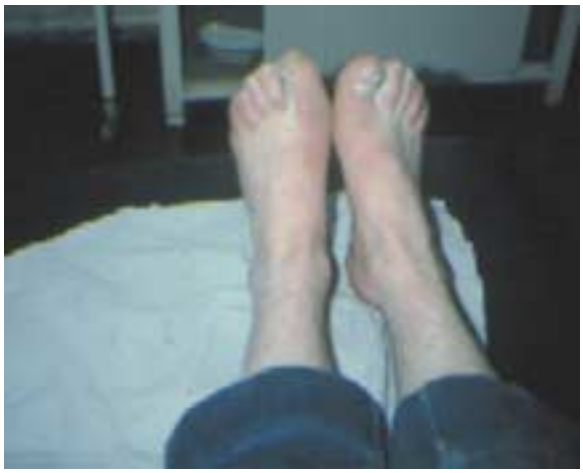

Fig. 15-6. Typical mild nonfreezing cold injury in a trainee British Royal Marine. This recruit had returned from a field exercise feeling well. While showering, his feet rapidly became swollen, red, and painful. (The white powder around his toes is foot powder, not rampant fungal infection.)

Second Stage: Following Cold Exposure

The second stage appears immediately following removal from the cold exposure environment and during or immediately following warming. The duration of this stage is typically fleeting, lasting only a few hours at most, although exceptional cases may persist for several days.

The postexposure stage is characterized by early small increases in peripheral blood flow as reperfusion of the ischemic tissues starts (see Figure 15-4). The extremities characteristically change color from white to mottled pale blue (see Figure 15-1), although pigmented skin may obscure these color changes (see Figure 15-5), while remaining cold and numb so that the individual may be unable to walk or maintain balance. The loss of sensory and motor function is often related to a pattern of anesthesia to pain, touch, and temperature, in any combination. Initial edema or swelling, or both, of the extremities is sometimes observed during this stage, and the peripheral arteries are often impalpable. Clinical assessment of neuromuscular function usually indicates an absence of sensory action potentials and a lengthening of distal motor latencies.

Third Stage: Hyperemia

The third stage of NFCI, hyperemia, in which the affected extremity receives increased blood flow,

may last for a few days to a few months, usually from 6 to 10 weeks in fully developed cases.

The third stage is quite distinct from the previous stages, and its onset is abrupt. During this stage the affected extremity becomes hot and flushed, with obvious redness (see Figures 15-2 through 15-6); these are among the most prominent signs of the progression of NFCI. The previously weak peripheral pulse changes to become full and bounding. The microcirculation appears sluggish, however, as illustrated by simple tests for capillary refill. A fingertip pressed onto the area to blanch the underlying skin will leave a white spot that persists for many seconds instead of disappearing rapidly (see Figure 15-7).

Anesthesia that was seen at stage two typically resolves during stage three. Intense pain is usually reported from the affected extremities, including hyperalgesia to the slightest touch. The persistence of the pain during the third and fourth stages, despite little overt tissue damage, is another outstanding and characteristic symptom of this injury. Many casualties report that the pain is worse at night, and it may deprive them of sleep. When NFCI occurs in the feet, pain is normally localized in the sole of the foot, typically across the base of the metatarsals, and may mimic metatarsalgia. Attempts to relieve the pain using conventional analgesics and antiinflammatory agents are usually completely unsuccessful; parenteral morphine merely removes the displeasure of painful sensation, but regional analgesia using local anesthetic may bring complete (if short-term) relief. Anesthesia in the most distal areas of the exposed extremities may still persist, however, in the face of this pain.

Edema frequently becomes obvious during this stage and in the most severely injured casualties, blisters containing serous or bloody fluid may form. In the rare cases severe enough to have suffered gross tissue damage, areas of skin may start to declare their nonviability before becoming overtly gangrenous in the next stage. Anhydrosis is often present at this time. This anhydrosis is not entirely predictable nor is its location, but often it is observed to occur in areas associated with sensory loss, particularly of warm sensation. Reflex vasomotor activity to both hot and cold stimuli is often absent. Clinical examination may demonstrate some loss of neuromuscular function and general muscle weakness. Diminished electrical excitability of the muscle has also been recognized during this stage.[11,12]

Fourth Stage: Following Hyperemia

The final stage of NFCI may last for weeks to months, in some individuals for years, and in some apparently for the remainder of their lives. However, stage four is remarkable for its lack of obvious physical signs. (Figure 15-8).

During this stage the previously observed inflammatory responses are usually reduced and limb temperature falls. The affected distal extremities remain cold, however, and demonstrate an increased sensitivity to cold stimuli, with prolonged vasoconstriction, in more than 60% of cases of NFCI.[3] Although milder cases may demonstrate normal vascular and vasoconstrictive tone at this stage, when any environmental or spontaneous event starts to cool the limbs, they may remain cold for many hours after removal of the initial stimulus. In some cases the injured extremities show a permanent temperature sensitivity. Usually these increased sensitivities are only in response to cold stresses, but rarely they may also be to heat. The long-lasting increase in temperature sensitivity, or "cold sensitization," is another prominent component in the progression of NFCI.

Persistent pain, often triggered by cold exposure and associated with vasoconstriction, has been reported in more than 70% of cases of NFCI and may be the dominant symptom.[3] Small areas of numbness may remain in perpetuity, although more substantial lasting sensory loss is unusual. Hyperhydrosis is found in a significant but smaller proportion of cases, and may provide a fertile environment for recurrent fungal infection. Such excessive sweating may be prompted by exposure to thermal stimulation, but interestingly, it may also often result from emotion. Shedding of the nail in affected digits is less common still, may become recurrent, and can progress to disturbances of nail growth such as onychogryphosis. The pathophysiological processes of the most severely affected casualties, who have dying tissues, will evolve similarly to those with gangrene from freezing cold injury (FCI; see Chapter 14, Clinical Aspects of Freezing Cold Injury), and all the long-term sequelae that have been reported following freezing injury can occur in casualties with NFCI alone.

The clinical investigation of fourth-stage NFCI is obviously of considerable interest and is discussed later in this chapter.

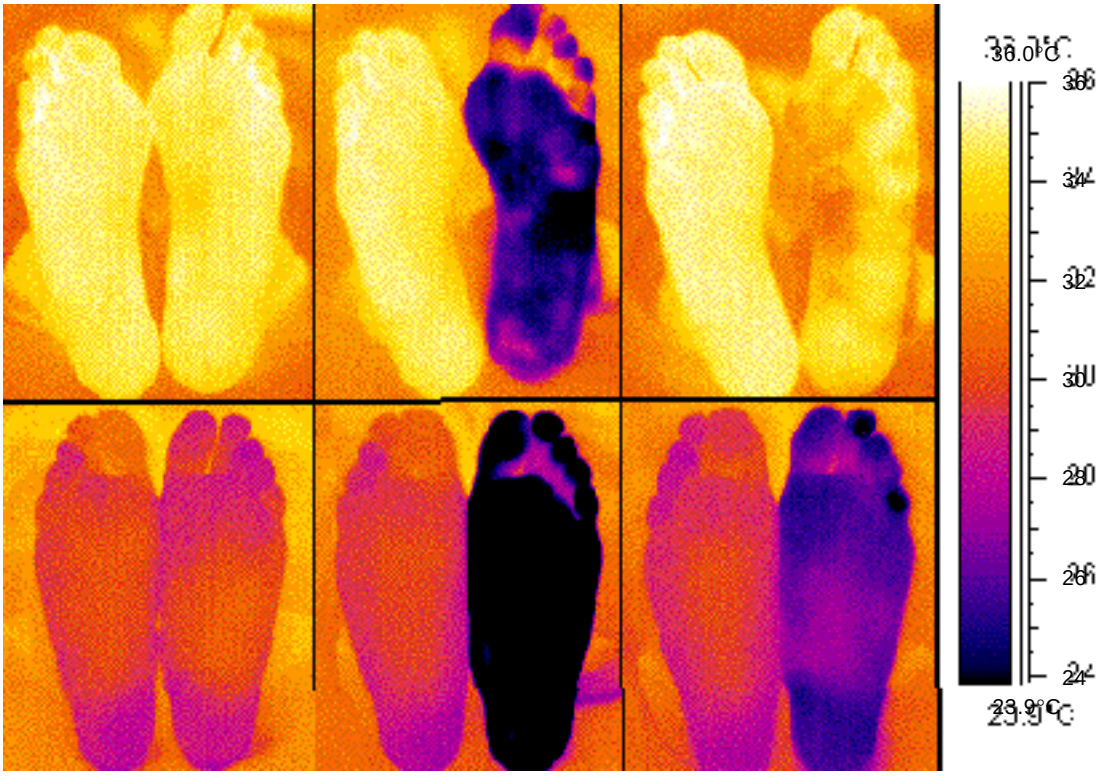

Fig. 15-8. Infrared thermography in the assessment of the consequences of nonfreezing cold injury. The upper sequence of three images was taken from an uninjured, asymptomatic control; the lower sequence from a patient who had sustained nonfreezing cold injury and was subsequently complaining of sensitivity to the cold. In both control and patient, the first (left) image was taken after resting in an ambient air temperature of 30°C. The second (center) image was taken immediately after the foot had been immersed in water at 15°C for 2 minutes. The final (right) image was taken 5 minutes after removal from the water, again in 30°C air.
The upper series shows feet that were warm at rest, which rewarmed briskly after mild cold stress, recovering almost completely within 5 minutes after removal from the water. The lower series shows a severe degree of cold sensitization: the feet were much colder than the surrounding air at rest, and once cooled, took a long time to rewarm, remaining much cooler than the control foot at 5 minutes after immersion. The scale at far right indicates the color–temperature relationship.

ETIOLOGY AND PATHOGENESIS OF NONFREEZING COLD INJURY

Although there is evidence that other tissues become damaged in nonfreezing cold injury, the site of primary injury appears to be the neuro-endothelio-muscular components in the walls of local blood vessels. Assumed for many decades to be a relatively simple system, more recent work on the modulation of neural control and non-neural regulation has shown that there are very sophisticated and interrelated regulatory mechanisms, any or all of which could be influenced by cold exposure and become disrupted as a consequence.

Vascular and Circulatory Pathology

The present view is that NFCI is brought about by intense and prolonged cold-induced peripheral vasoconstriction. Although contributions from direct cold effects on neural function and from reperfusion following ischemia often complicate the injury development, the majority of clinical and experimental studies to date suggest that intense vascular activity is an initial and most significant feature in the etiology of NFCI.

In addition to the present view regarding the potential role of cold-induced *vasoconstriction* in the etiology of the injury, clinical and experimental studies are consistent in showing that cold-induced *vasodilation* (CIVD) often disappears quite early during initial cold exposure. The observed elimination of the CIVD response indicates the profound effect prolonged peripheral vasoconstriction may have in the development of NFCI. The loss of control over peripheral vasodilation may be one of the early mechanisms involved in the onset of NFCI. Recent research has confirmed experimentally the reduction or elimination of CIVD during prolonged cold exposure.[16,17]

Francis and Golden[1] have presented an excellent summary of the etiological factors related to the development of NFCI and an overall conceptualization of the interrelationship among those factors. An updated schematic description of their conceptualization is shown in Figure 15-9. At the core of the diagram is the concept of vasoconstriction as a major modulator in the development of NFCI. Other critical etiological factors contribute to the sympathetic tone that in turn directly relates to peripheral vasoconstriction. In reviewing various classic and contemporary research articles on the pathogenesis of NFCI, Francis and Golden suggest that the most important mechanism is the "vicious circle" of cooling and vasoconstriction associated with a high level of sympathetic tone, which no longer can be affected by CIVD. They also conclude that it is now important to direct research efforts toward the prevention of NFCI and that as the central focus of any research effort on the prevention of NFCI, it is important to consider how the vicious circle can be broken.

The Roles of Circulating Vasoactive Substances

Norepinephrine, whether circulating in the peripheral blood or released from sympathetic nerve endings, induces constriction of vascular smooth muscle. It is well established that the vasoconstriction is primarily mediated by the activation of sev-

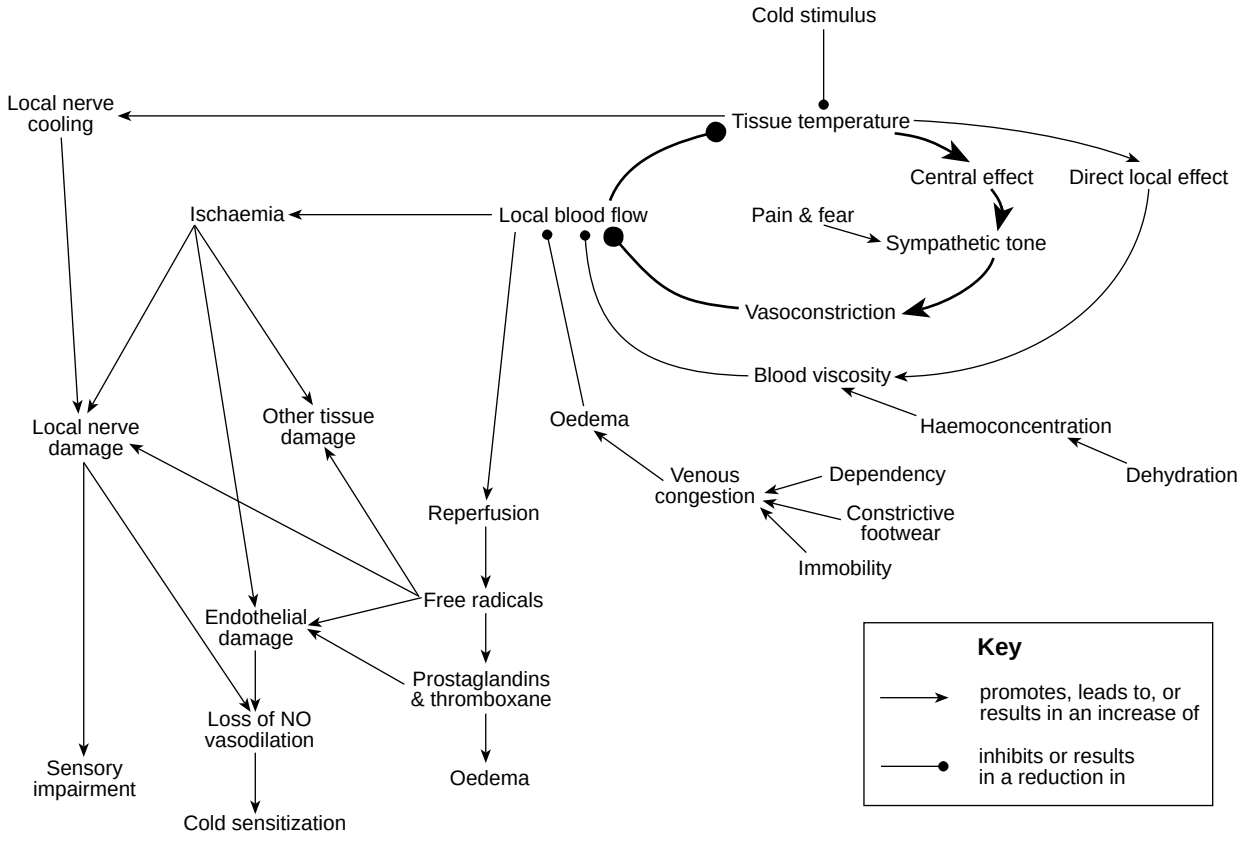

Fig. 15-9. Schematic diagram illustrating the postulated etiological factors and mechanisms of the pathogenesis of nonfreezing cold injury. Adapted and updated with permission from Francis TJR, Oakley EHN. Cold injury. In: Tooke JE, Lowe GDO, eds. *A Textbook of Vascular Medicine*. London, England: Arnold; 1996: 360.

eral subclasses of α-adrenergic receptors.[18] At present there is still lack of agreement regarding the role of specific receptor subclasses in cold-induced vasoconstriction in different tissues, but experimental evidence indicates that α_2 receptors play a prominent part.[19]

Exposure to cold temperatures has been demonstrated to stimulate the release of norepinephrine in the peripheral circulation by as much as 300%,[20,21] leading to intense and prolonged peripheral vasoconstriction. Cold-induced peripheral vasoconstriction often lasts quite long due to additional modulation of norepinephrine levels. Cold reduces the rate of uptake and metabolism of norepinephrine that results in continued vasoconstrictor stimulation.

Cold temperatures have an additional direct effect on the walls of blood vessels that contributes to prolonged vasoconstriction. The initiation of the vasoconstriction response involves an increase in the concentration of cytosolic-free calcium. Depending on tissue specifics, the calcium source can be intracellular, extracellular, or both.[22] Additionally, during exposure to cold, blood flow to the skin is reduced owing to the increase in sympathetic tone and the direct sensitizing effect of cold on the cutaneous blood vessels.[23] Cutaneous vasoconstriction reduces heat loss by redirecting blood from the vasoconstricted cutaneous vessels to deeper vessels, where more favorable heat transfer takes place. However, research indicates that although adrenergic involvement is of major importance, other neurotransmitters and peptides play perhaps more important and modulatory roles in cold-induced peripheral vasoconstriction.

Cold-Induced Ischemia

As previously mentioned, a prevalent view of NFCI is that it is a vascular neuropathy brought about primarily by intense and prolonged cold-induced peripheral vasoconstriction. Although numerous nonvascular components are obviously involved in the development and symptomatology of NFCI, alteration in peripheral blood flow in the cutaneous circulation is commonly a salient feature.[2,11,12] Landmark clinical descriptions of NFCI by Ungley, Channell, Richards, and Blackwood,[11,12] based on numerous observations, recognized the major role of cold on peripheral blood vessels in the development of NFCI. In addition to their observations indicating that intense peripheral vasoconstriction is of prime importance in the etiology of NFCI, these investigators also concluded that some of the most severe damage to minute cutaneous blood vessels occurs during the time of cold exposure. Their findings indicated that although a complex sequence of events may follow, initial vascular involvement may be paramount in the onset of NFCI.

In addition to the insults precipitated by reduced blood flow due to vasoconstriction, tissue damage is also associated with the cold-induced vasoconstriction. Recent studies[17] have observed prominent endothelial injury during cold exposure, particularly the opening of junctions between adjacent endothelial cells. Also observed during cold exposure is the adhesion of leucocytes to the small blood vessel walls and occlusion of blood vessels due to the accumulation of blood cells.[17] The pronounced microvessel constriction and reduced blood flow lead eventually to local tissue hypoxia, which, in turn, complicates the injury.

Cold-Induced Vasodilation

If, during initial exposure of an extremity to cold, a predominant response is restriction of peripheral blood flow due to sympathetic vasoconstriction, then we might expect peripheral vasoconstriction to continue—even after the temperature of the tissue reaches that of the surrounding environment. Instead, however, a complex and dynamic vascular response usually occurs. As the exposed extremity continues to cool, the peripheral circulation usually passes through a phase of cold-induced vasodilation (the CIVD response),[24] which is believed to be a protective mechanism against damage to peripheral tissues. The observed vasoconstriction-vasodilation oscillation of blood flow in the extremities exposed to cold may continue for several hours.[25] Experimental evidence is consistent with the hypothesis that the initial cold-induced vasoconstriction is produced by an enhanced smooth muscle responsiveness to norepinephrine, whereas CIVD is related to a cessation of the transmitter release from adrenergic nerve endings.[26] There is an alternative claim, however: that the vasodilation results from a cold-induced relaxation of vascular smooth muscle.[5] It is generally considered that intense cold-induced vasoconstriction results in a reduction of blood flow to the distal tissues. As the temperature of the tissues drops, sympathetic nerve conduction is interrupted and vasodilation occurs owing to the cessation of norepinephrine release. The resultant return of blood flow rewarms the tissue, nerve conduction is reestablished, norepinephrine is released, and renewed vasoconstriction occurs.[27]

As important as CIVD appears to be as a protective mechanism against damage to peripheral tissues, it is equally important that the absence of the CIVD response may be a significant component in the development of NFCI. CIVD may be considerably delayed in onset or completely abolished in the presence of high levels of vasoconstrictor tone.[28] The diminution of the CIVD response has been suggested as potentially involved in the development of NFCI.[1,2] In an animal model of NFCI following a cold injury exposure, CIVD was found to be completely absent and remained absent for several weeks, suggesting that CIVD loss is indeed associated with the development of NFCI.[16] The observed elimination of the vascular response after prolonged cold exposure may indicate the profound effect that prolonged peripheral vasoconstriction can play in the development of NFCI. Direct microvascular observations[17] have also indicated rapid loss of CIVD during cold exposure.

Neural Pathology

Clinical and experimental studies alike have indicated that cold exposure can be a direct cause of peripheral nerve injury. Nerve dysfunction and later prolonged damage to peripheral nerves and to sympathetic fibers are common components of severe NFCI. A widespread, predominantly distal degeneration of axons has been documented as a result of exposure to cold.[29] Historically, there has been general disagreement on the pathological changes in neural tissues as a consequence of NFCI, particularly evidence regarding degeneration of nerves. Early observations[30] suggested that small and unmyelinated nerve fibers were most affected by cold, and that large myelinated fibers tended to survive cold exposure. Other observers[31,32] made the opposite suggestion; that small myelinated and unmyelinated fibers tended to survive cold exposure, and large myelinated fibers have the greatest susceptibility to cold. In numerous studies, no relationship was obtained between the size of the nerve fiber and its susceptibility to cold damage. Certainly, research protocols and species differences contributed to the contradictory observations regarding cold-induced nerve injury. The weight of more-recent research[1,33] has tended to demonstrate that thick, myelinated fibers appear to be more susceptible to damage by cold. However, the full extent of fiber involvement probably depends, ultimately, on the actual duration and severity of the cold exposure. Additionally, there is consistency in studies that indicates that cold exposure results in nerve conduction blockage and associated cessation of axoplasmic transport.[33] Often nerve edema is present, and passive leakage through damaged endoneurial capillaries occurs. Although the mechanisms directly responsible for cold-induced nerve damage are far from clear, it is considered likely that ischemia plays an important role in the etiology of the nerve injury.

Some research using animal models has shown changes in muscle and blood vessels following cold exposure,[30,34] suggesting that NFCI may be related to changes in supporting vasculature leading to nerve ischemia, whereas other studies[29,35,36] have shown peripheral nerve degeneration without apparent damage to blood vessels. It appears that the mechanism of nerve damage by NFCI is complex and may depend upon the general procedure used to induce the cold injury. For example, in those experiments mentioned above,[29,35,36] in which extremities were cooled and no changes in blood vessels were observed, the animals were anesthetized during cold exposure. In other studies[30,34,37] in which blood vessel damage was reported, the animals were conscious during cold exposure. It is possible that the added stress associated with the cold exposure in awake, conscious animals may provide a component to NFCI that leads to blood vessel changes and nerve ischemia. It is important to note that nerve fiber damage is often located in proximity to vascular elements rather than to peripheral nerve areas. This may indicate that neural pathology is not always due to direct cold effects on neural tissue, per se, but can be confined to areas of cold-induced vascular dysfunction.

Stress and Nonfreezing Cold Injury

Although NFCI is clearly related to sustained exposure of extremities to a cold environment, mere cold exposure of an extremity often does not appear to be sufficient to produce the clinical symptomatology and pathology in humans. This might distinguish NFCI from other forms of local cold injury (eg, frostbite). The pathogenesis of NFCI includes not only exposure of the extremities to cold for an extended period, but often a confluence of factors that, together with cold exposure, appear to facilitate the formation of the distinctive pathology.

Evidence collected from military cold research indicates that cold injury appears to occur more

often among military personnel in combat situations than in civilians or in noncombat military personnel exposed to similar or even more severe cold weather.[4,6,7] This differential occurrence suggests that the conditions existing in warfare environments somehow interact with exposure to cold weather to potentiate NFCI. Numerous studies conducted during World War II and the Korean War suggest that combat stress was a significant contributing factor in cases of cold injury.[7,38–41] The physiological changes incurred in stressful combat conditions may alter peripheral thermoregulatory mechanisms during cold exposure and thereby promote the formation of cold injury in the extremities.[1,7] Although there is a very strong suggestion that stress exposure may influence the susceptibility to NFCI, little attention has been given to the manner in which stressful stimuli may modify physiological responses to cold.

Behavioral stressors such as cold exposure can also profoundly affect vasomotor tone.[42–44] Acute and prolonged stress resulting from exposure to combat environments results in significant peripheral vasoconstriction, particularly in the extremities.[1] Moreover, physiological reactions associated with combat stress, such as sweating, combined with intense vasomotor constriction can lead to temperature reduction, especially in the distal portions of the hands and feet—the parts of the body that are most susceptible to NFCI. Behavioral stress dramatically affects the peripheral circulation in a manner similar to that observed when an extremity is exposed to a cold environment. Changes in peripheral circulation that accompany or result from either an acute or a prolonged stress-inducing environment may worsen the physiological conditions in an exposed limb and facilitate the conditions for the development of NFCI.

Reperfusion Injury

In recent years, there has been considerable interest in molecular mechanisms of injury that occur during the reperfusion of vascular beds that have been ischemic for prolonged periods. Although the vast majority of such studies have focused on other tissues and forms of insult, Das, Iyengar, Jones, Lu, and Maity[45] have provided good evidence that the administration of agents that inhibit the generation of toxic oxygen substances can attenuate the damage caused by NFCI. This is in accord with the rationale behind slow rewarming (discussed below in Treatment of Nonfreezing Cold Injury), which is based on the observation that rapid rewarming of NFCI exacerbates the injury. Although it is fair to conclude that reperfusion injury is an important component of the etiology and pathogenesis of NFCI, it is not yet possible to compare its importance with other components.

Ischemic-Hyperemic-Sensitization Disorders

Clinically, NFCI appears to be a somewhat indistinct member of a family of disorders in which there are different combinations of ischemia followed by hyperemia and subsequent sensitization to temperature disturbance. Other conditions in this group may be barely distinguishable from NFCI and have obvious common etiological factors, or they may appear to be more distinct. For example, "shelter limb" occurred in civilians who were forced to take shelter in the deep tunnels of the London Underground during the blitz in World War II.[46] Clinical descriptions of shelter limb are indistinguishable from the characteristic stages of NFCI, so it appears to be closely related. Another condition that resembles NFCI is "paddy foot," which occurs in military personnel whose feet are immersed for prolonged periods in much warmer water (typically warmer than 24°C).[47] Remarkably, some casualties who suffered NFCI in the Falkland War went on to suffer 100% incidence of paddy foot when they were later sent to train in tropical jungles. Another interesting condition that is possibly identical to NFCI is "pink disease," in which children who sleep with their hands and feet exposed to cold room air present as apparently stage-three NFCI. It has been suggested that childhood pink disease may account for some of those fresh military recruits who seem unusually susceptible to the cold.

More-distant relatives of NFCI may include another apparently protean group of conditions now known as the reflex sympathetic dystrophies (RSDs). Although extremely variable in presentation, many RSDs follow blunt tissue trauma such as that sustained in automobile accidents, in which prolonged reduction in local nutrient flow could have occurred. Later, these patients may complain of swelling, pain, and sensitivity to temperature (warm, cold, or both). Attempts to treat RSD by sympathectomy are also variable in success. One promise of continued research into NFCI is that the results may also be of benefit in addressing these other, possibly related, conditions.

EXPERIMENTAL AND RESEARCH APPROACHES TO NONFREEZING COLD INJURY

Laboratory animal studies of NFCI have been performed in order to better understand the development and pathophysiology of the injury, which in turn, might ultimately lead to more successful prevention. Clinical human research has focused on the development of technologies to investigate salient characteristics of NFCI.

Animal Models

Numerous laboratory animal studies have focused on the constellation of dysfunctions associated with exposures to nonfreezing cold. Briefly detailed here are selected animal studies that highlight various focuses of research that have been considered central in attempting to understand the etiology of NFCI.

In one of the earliest research papers, Smith, Ritchie, and Dawson[48] exposed rabbits to wet and dry cold. These investigators reported that primary damage immediately after cold exposure was to capillary vessels, with no observed damage to nerves or muscles of the extremities. Later, an extremely influential experimental investigation of NFCI was performed by Blackwood and Russell,[30] using the rat tail as the research model. In this study there was an attempt to expose the animals to wet, cold conditions comparable in many respects to those under which NFCI develops in humans. Caged animals were systematically exposed for 24 to 96 hours to 3°C to 4°C air temperature, with 4°C to 5°C water running through and filling the cages to a depth of 1 in. The animals were then examined immediately and up to 60 days later. Following exposure, different animals were rewarmed at different rates. This study is of interest because it is one of the few that tried to mimic the conditions of human exposure and then followed the course of injury development over an extended period of time. These investigators found damage to nerve and muscle tissue after exposures of 48 hours, and the intensity of the damage increased with longer exposures. In animals examined 2 months after exposure, the nerve and muscle tissue still showed evidence of degeneration. It was observed in this study that the primary injury appeared to occur during the exposure, and that variations on the rewarming process had no systematic effect on the ultimate pathology.

Lange, Weiner, and Boyd[49] exposed the hind leg of rabbits to 3°C to 5°C cold water for 3 to 4 days. They, like Blackwood and Russell, also observed dysfunction mainly in muscular and nervous tissue. Capillary permeability increased and severe edema formed during, rather than after, exposures.

Das and colleagues[45] studied the effects of cold exposure and focused primarily on aspects of rewarming in rabbits. The legs of rabbits were exposed to a freezing mixture of ice and salt at 0°C for 20 minutes. Cellular injury during cold exposure and rewarming was monitored by estimating the release of creatine kinase and lactate dehydrogenase in plasma samples obtained from the femoral artery. These markers showed a slight increase during cooling but a marked increase during rewarming. The injury obtained in this study was believed due to the generation of oxygen-derived free radicals that may attack membrane phospholipids during rewarming, as significant breakdown of membrane phospholipids was observed. Interestingly, administration of quinacrine, a phospholipase inhibitor, preserved membrane phospholipids and reduced the release of the intracellular markers of injury.

Many of the research studies relating to NFCI have focused experimentally on the particulars of the neuropathies resulting from cold exposure. Denny-Brown and colleagues[31] investigated the effects of 0.5°C to 8°C cold exposure on the sciatic nerves of cats. This was one of the first studies that clearly demonstrated that cold exposure selectively damages the peripheral nerves of the extremities, in that large myelinated fibers were found to be more susceptible to cold-induced damage than smaller ones. These investigators demonstrated that exposures as short as 30 minutes at 8°C could produce nerve damage. The similarity of the damage to that related to vascular ischemia was noted.

Peyronnard, Pedneault, and Aguayo[29] submerged rats up to hip level in 1°C cold water for 12 hours and then examined ventro-caudal nerves at varying time periods following cold immersion. The rat tail nerves examined showed a greater loss of large myelinated fibers than of myelinated fibers of lesser diameter. Unmyelinated fiber numbers remained within the range of controls.

Experimental cold injury to the sciatic nerves of rats was studied by Nukada, Pollock, and Allpress.[33] Cooling of the nerve was accomplished by circulating 3°C cold water through copper tubing on which the exposed nerve was placed for 2 hours. They found nerve conduction block and termination of axoplasmic transport. Prominent nerve edema was observed with damaged endoneurial capillaries and

a widening of endothelial junctions. Large myelinated nerve fibers were severely damaged, whereas unmyelinated fibers were not affected. The authors of this study suggested that the nerve fiber degeneration they observed may be related to cold-induced blockage of axoplasmic transport.

Gilliatt and Kennett[50] studied the effects of cold exposure in the tibial nerves of rabbits. The hind limb was immersed up to the lower thigh in 1°C cold water for 10 to 14 hours, or the exposed tibial nerve was placed in a cooling trough maintained at 5°C for 2 to 3 hours. These investigators observed local axonal injury that eventually led to Wallerian degeneration. After 3 to 4 weeks they found loss of large myelinated fibers with no effect on nonmyelinated fibers.

The effects of cold temperature on peripheral nerve function and structure were studied in rats by Shurtleff and colleagues.[37] The tails of rats were submerged in 1°C cold water for 10 to 12 hours. Nerve action potentials and muscle action potentials in the tail were altered following cold exposure. Reductions in potential amplitudes were observed immediately after cooling, with further reductions over the week following exposure. Initial nerve damage appeared to be located just below the surface of the water, and later, in the first week after exposure, Wallerian degeneration occurred. Damage was observed in large myelinated fibers and capillaries following cold exposure. The capillaries within the endoneurium showed unusual endothelial and red blood cells, and many had occluded lumina. The pattern of damage suggested a vascular component in the injury.

The effects of cold exposure on thermal sensitivity were investigated by Ahlers and colleagues.[51] Thermal sensitivity was measured in the tails of rats before and after the tail and a portion of the hind flank were exposed to 1°C to 4°C water for 1 to 9 hours. They found that exposure of the rats to cold water for 6 to 9 hours produced anesthesia at first, followed by a heightened temperature sensitivity to a heat stimulus to the tail. Although the animals initially exhibited increased latencies in tail-withdrawal responses immediately following the cold exposure, on subsequent sessions they showed an increased sensitivity to the heat stimulus, indicated by decreased latencies in tail withdrawal. The course of alterations in thermal sensitivity obtained in this study appears broadly similar to those observed in humans with NFCI.

Thomas and colleagues[16] studied alterations in cutaneous blood flow and temperature in the tails of rats immersed in 1°C cold water for 6 to 9 hours. Following cold exposure, cold-induced vasodilation was absent and remained absent for several weeks. Cold-induced disturbances of cutaneous blood flow in the rat tail consisted of a sequence of distinctive stages, analogous to those observed in human NFCI. Immediately following cold exposure of several days, reduced blood flow and thermal sensitivity were observed, followed in a week by a hyperemic stage, and later by increased vascular and thermal sensitivity.

These selectively reviewed studies, as well as others, clearly suggest that there is a significant vascular component associated with the development of NFCI, probably directly involved with cold-induced vasoconstriction or cold-induced ischemia. The research literature also seems consistent in indicating that most neural damage occurs in larger myelinated fibers, probably resulting from a complex interaction of direct cold effects and damage to supporting neural vasculature. Generally, Wallerian degeneration occurs in the more distal parts of the affected fibers at a later time.

Although the summary of these individual and collective findings brings appreciation of much information regarding the pathology of the cold injury, it should be emphasized that most of these studies have examined the effects of application of a cold environment to a specific system injury. However, with only a few exceptions, the results of these animal studies are not necessarily directly pertinent to the unique human NFCI condition, as the majority of the studies do not indicate a discernible progression of stages following cold exposure that are analogous to the syndrome as described in humans.

Human Studies

The great majority of earlier work on the pathophysiology of NFCI in humans concentrated on the gross injuries seen during the two World Wars. Although pathological examination of amputated limbs led to detailed descriptions of such severe injuries, it (*a*) has not provided useful insight into more pervasive subtle injuries and (*b*) has produced conflicting conclusions. Because it would be manifestly unethical to experimentally induce NFCI in human subjects, more recent attention has been directed at the investigation of cases during the fourth stage, principally to gain insight into the mechanism by which the combination of cold, ischemia, and reperfusion can result in prolonged cold sensitization.

Clinical observations led Francis and Golden[1] to advance the hypothesis that cold sensitization resulted from sympathetic denervation supersensitivity, which in turn, was caused by local damage to

the sympathetic fibers innervating the peripheral vasculature. As Oakley[52] pointed out, this would imply either that NFCI was selectively affecting small and unmyelinated nerve fibers, or that those fibers were being damaged along with others but were least able to regenerate successfully. His results from the measurement of thermal sensory thresholds confirmed the relative sparing of larger and myelinated fibers, in direct conflict with most observations in animal experimental models. In a later review, Francis and Oakley[3] highlighted the many conflicts raised by the hypothesis of denervation supersensitivity.

The next step was to use more careful experimental measurements of skin blood flow, obtained using modern laser Doppler rheometry, to study the altered pattern of local vascular responses. Initial results suggested that there was no evidence to support the existence of sympathetic denervation supersensitivity, but that there may have been an underlying abnormality of the local vascular endothelium.[48] However, most recent work has shown that responses to a wide range of maneuvers are normal despite gross cold sensitization; this makes it extremely unlikely that there is any significant lasting nerve damage, and rules out Francis and Golden's hypothesis. The only significant and consistent abnormalities found in the microcirculation of those with stage-four NFCI were (*a*) greatly reduced resting flows and (*b*) exaggerated responses to a cold stress. Both "on" and "off" responses to maneuvers believed to be modulated by local sympathetic action were unaffected by injury. Future studies are intended to observe the effects of iontophoresis of various vasoactive agents into the distal extremities of those with cold sensitization.

Synthesis of these findings is difficult, particularly as such a profound vascular consequence appears to have little physical evidence to account for it. There are two additional mechanisms that have not yet been studied in humans or animals. The first is that early sympathetic and endothelial disruption is followed by regeneration and peripheral recovery, but that higher control mechanisms are altered during this period to produce the characteristic sensitivity to cold. The second is that early responses to the injury result in a transient physiological sensitivity to the cold, possibly as a result of sympathetic injury, which results in a reduction in the number of vessels in the microcirculation—the opposite of the vascular proliferation seen during physical training and heat exposure. Either process could then be self-reinforcing through Francis and Golden's vicious circle of cooling.[1]

A range of different techniques have been used to investigate fourth-stage NFCI, of which infrared thermographic assessment of sensitivity to the cold and the measurement of thermal sensory thresholds appear to be the most useful. Infrared thermography was introduced in the United Kingdom by Golden, during his studies of veterans of the Falkland War in 1982, and was later taken up in the United States by Hamlet. Two completely different protocols have developed as a result. In the United Kingdom, patients are subjected to a local standardized mild cold stress (currently, 2-min immersion in a waterbath at 15°C) after the rest of the body has become accustomed to a warm air temperature (30°C). Thermograms taken immediately prior to, immediately following, and 5 minutes after removal of the hand or foot from the water are then used to assess resting limb temperature and the speed of recovery of that temperature (see Figure 15-8). By contrast, in the United States, the protocol attempts to assess CIVD in a limb exposed to more-prolonged and -severe cold exposure. British experience with the latter approach was discouraging, owing to the difficulty in reproducing CIVD responses even in ostensibly normal subjects.

More recently, Oakley and Lloyd[53] started using the Middlesex Hospital Thermal Testing System, a simple automated process designed to measure warm and cool sensory thresholds in patients with diabetic neuropathy.[52] They found that unrecordably high warm sensory thresholds, more than six Centigrade degrees above the skin temperature of the affected body part, were extremely common in patients with NFCI although never found in healthy controls. Although not a directly relevant assessment of cold sensitization, unlike thermographic assessment, this automated process is now in routine use as a discriminatory test. Oakley[54] has also measured skin blood flow in affected limbs using laser Doppler systems, but this is time-consuming and normally contributes little that could not be obtained from thermography.

TREATMENT OF NONFREEZING COLD INJURY

Currently, treatment consists of the application of fairly obvious and simple interventions. Research may yet provide leads to more specific, no doubt pharmacological, interventions.

Hypothermia

If an individual who has developed NFCI has been exposed to a cold environment long enough, there is always the possible complication of hypothermia. The appearance of hypothermia is a medical emergency and may make the diagnosis and treatment of local cold injury more difficult. A major concern if hypothermia is present is modulation of the treatment relating to rewarming of the individual. NFCI requires a very gradual rewarming of the injured extremities, while hypothermia may require rewarming of the body as rapidly as is possible. Owing to the potential life-threatening aspects of hypothermia, treatment of that condition takes precedence over the problem of NFCI, of course, although the extremities should be spared if NFCI is suspected.

Warming

In cases of NFCI, affected extremities should be allowed to rewarm slowly. In fact, rapid rewarming may actually intensify the injury. Often, it may be preferable during earlier stages of NFCI, if appropriate, to transfer the individual to a more comfortable rewarming site, without attempting to rewarm in the immediate cold environment.

Dehydration

If an individual has been exposed to cold for more than a day, it can usually be assumed that dehydration is present, a consequence primarily of cold diuresis. Individuals should be rehydrated as soon as possible if evidence of dehydration is apparent. Rehydration with warm liquids is an essential aspect of any rewarming regimen, and is also a major contributor to the stabilization of normal physiological processes and the modulation of critical cold-induced fluid shifts within the body. Rehydration will also contribute to more adequate blood flow in the extremities of the cold-exposed individual.

Tissue Freezing Complications

Clinical evidence suggests that in severe cold exposures, the tissues of an individual may have passed through cycles of frostbite in addition to exposure to conditions that induce NFCI. In such cases, careful diagnosis as well as attention to the specifics of combined injury treatment are required.

Drug Treatment

At present, no known medications have been specifically identified as appropriate for the treatment of NFCI once the critical exposure duration has been reached. Because of the known involvement of α-adrenergic receptors in the control of peripheral limb circulation and the observed noradrenergic sensitization of individuals with NFCI,[1] it was believed previously that administration of α-adrenergic blocking agents or general vasodilators would be beneficial. However, this approach to treating NFCI is of little help. Presently, the most that pharmacological intervention can offer a casualty with NFCI is a reduction of the symptoms related to persistent pain.

Physical Therapy

If the individual's condition warrants such treatment and the facilities are available, physical therapy can be beneficial in the treatment of NFCI. Physical therapy during the early stages of NFCI can help maintain adequate joint articulation in cold-exposed limbs. Exercises of the legs, ankles, and feet may be of immense treatment support. If physical therapy is started during the early stages of NFCI, then it is usually indicated that it be continued through the later stages.

Pain Treatment

Pain is often one of the most enduring features associated with NFCI and can persist throughout the later stages. Unfortunately, the treatment of this pain remains controversial. As described earlier, conventional approaches have been singularly unsuccessful, and cannot be recommended. In a pilot study in 1980 and 1981, Oakley used quinine salts (200–300 mg, given at night), which appeared more successful than regular analgesics, although others since have denied that they are of use. Since 1982, the standard treatment in the armed forces of the United Kingdom, first proposed by Riddell,[55] has been amitriptyline hydrochloride, in doses of 50 or 100 mg given at bedtime. Incremental increases in dosage may be required with both drugs if pain "breaks through" after initial relief.[3]

Sympathectomy

Surgical or pharmacological disruption of the regional sympathetic nerve supply has long

been advocated for the treatment of increased sensitivity to the cold and persistent pain. However, the rationale behind this remains elusive, and there is a dearth of reported studies that use controls or follow treated groups for sufficient periods of time. In recent experience, sympathectomy may give short-term improvement in local perfusion and attenuate increased sensitivity to the cold. Some subjects also report impressive pain relief. But by 6 months later, these signs and symptoms have usually returned to their previous severity, if not actually worsened. No form of sympathectomy can therefore be recommended as having any lasting clinical merit, and clinicians should avoid becoming enthused by initial responses to trials of nerve blocks.

PHARMACOLOGICAL RESEARCH CONSIDERATIONS

Although at present there are no pharmacological interventions that are directly applicable to the prevention of NFCI, recent research related to vascular and neural pharmacological considerations certainly suggest areas that appear promising for concentrated research efforts.

Vascular Considerations

The evidence presented here supports a view of the importance of prolonged cold-induced peripheral vasoconstriction in the etiology of NFCI. The critical events that initiate the injury appear to occur during the time of cold exposure rather than following it, although there are obvious complications in the injury development from reperfusion following ischemia and from the direct effects of cold on neural function. The existing clinical and experimental observations on NFCI indicate that the magnitude and duration of cold-induced vasoconstriction are often far more intense than might be accounted for by sympathetic nerve activity, as reflected by adrenergic activation. As discussed earlier, adrenergic blocking agents and vasodilators have had little success in the prevention or treatment of NFCI. It is apparent that other major factors contribute to profound cold-induced vasoconstriction besides the vasoactivity mediated by known adrenergic involvement.

In this regard, several vasoactive peptides have been identified in the peripheral nervous system; they possess (*a*) some of the most profound vasoconstrictor activity known in humans and (*b*) the capability to interact with adrenergic activity. The vasoconstrictor activity of these vasoactive peptides occurs through their own receptors as well as through synergistic interactions with the adrenergic system. That is, the vascular activity induced by norepinephrine may be potentiated by enhanced circulating or local concentrations of these peptides. More important, these peptides are now known to be released in response not only to cold environments but also to other stressful environments.

Neuropeptide Y is a 36-amino acid peptide neurotransmitter[56] with a wide distribution in the peripheral nervous system.[57–59] The actions of neuropeptide Y at sympathetic neuroeffector junctions have occasioned numerous studies, owing to the prevalence of the peptide in sympathetic nerves and its coexistence with norepinephrine in these nerves.[58] At least three important effects of neuropeptide Y have been demonstrated at sympathetic neuroeffector junctions[60–62]:

1. a direct postjunction response, such as that of vasoconstriction;
2. a postjunctional potentiating effect of norepinephrine-evoked vasoconstriction; and
3. a prejunctional suppression of stimulated norepinephrine release.

It has been suggested that the vasoconstrictor activity of neuropeptide Y becomes more important during situations of high sympathetic nerve activity, such as exposure to cold.[63] Increased sympathetic nerve activity, such as that due to cold, is accompanied by both adrenergic desensitization and increased neuropeptide Y release.[63,64] Thus, neuropeptide Y may restore lost responsiveness to norepinephrine, and neuropeptide Y may also become a more efficacious vasoconstrictor agent. Indeed, neuropeptide Y is capable of constricting small arteries enough to produce total ischemia.[65]

In a study in which rats were exposed to 4°C water for 10 minutes, circulating neuropeptide Y levels were increased by 300% and remained elevated for 30 minutes following the rats' removal from the cold.[66] This study demonstrates the long-lasting effects of neuropeptide Y that have been associated with its extended vasoconstrictor response. More importantly, this study found that during chronic exposure, neuropeptide Y effects did not become habituated, as is usually found for catecholamine responses, but actually increased in magnitude. Additionally, it has been observed that central administration of neuropeptide Y can induce profound peripheral vasoconstriction, demonstrat-

ing that central neuropeptide Y release may be an important contributor to the stress-induced enhancement of NFCI.

Endothelin 1, one of the isoforms of endothelin, has been shown[67,68] to be a highly effective vasoconstrictor that evokes potent and long-lasting constriction effects. Other forms of the endothelin peptide are now known to possess vasoactive activity; however, the vasoconstriction potency of endothelin 1 is reported to be 20-fold greater than that of norepinephrine, making it one of the most potent human vasoconstrictors known.[69] Relevant to the development of NFCI, increased release of endothelin 1 has been observed in humans during cold stress.[70] Importantly, endothelin 1 has been demonstrated to interact synergistically with neuropeptide Y to induce rapid, intense, and long-lasting vasoconstriction.[71] More relevant to the etiology of NFCI, combinations of increased sympathetic tone, increased circulating endothelin 1, and increased circulating neuropeptide Y levels can promote increased expression of prolonged α-adrenergic receptor and neuropeptide Y-mediated regional vasoconstriction in altered conditions, such as those induced by cold.[71]

In addition, an important role in vasoconstriction induced by cold exposure has been identified for 5-hydroxytryptamine (ie, seratonin).[72] In particular, the vasoactive response of 5-hydroxytryptamine to cooling appears to be mediated by the 5-hydroxytryptamine$_2$ receptor.[72,73] The role of 5-hydroxytryptamine$_2$ receptors in cold-induced peripheral contractions has been clearly identified in humans.[72] The contribution of the release of 5-hydroxytryptamine during cold exposure is potentially even more important in cold-induced vasoconstriction, because 5-hydroxytryptamine and neuropeptide Y have been shown to interact synergistically to induce significant vasoconstriction.[71] Also, like endothelin 1, 5-hydroxytryptamine can induce vasoconstriction by neuropeptide Y with concentrations of neuropeptide Y that alone do not produce constriction.[71]

One of the most important sequence of events in the etiology of NFCI appears to be related to the initial changes induced by intense and long-lasting peripheral vasoactivity during cold exposure. It would appear that one of the most appropriate places to try to break the vicious circle of cooling and vasoconstriction described by Francis and Golden[1] is at the initiation of cold-induced vasoconstriction. Such an approach would be consistent with evidence from both clinical and experimental studies indicating the paramount importance of severe peripheral vasoconstriction in NFCI; this approach also indicates that biotechnologies that focus on the alleviation of intense cold-induced vasoconstriction could be important in preventing NFCI. An understanding of (*a*) the role of the vasoactive peptides, such as those discussed above, that are released during cold exposure; and (*b*) their vasoconstrictor effects as mediated through their own receptors, as well as through synergistic interactions among themselves and with the adrenergic system, may lead to the development of technologies that prevent NFCI.

Relevant to this consideration, specific antagonists for these potent cold-induced vasoactive peptides are now available, making pharmacological intervention possible that would completely or partially block cold-induced vasoconstriction activity. These antagonists offer a promising class of agents to be examined for potential prevention and treatment of NFCI. Current knowledge suggests that such antagonists could, in theory, modulate the role of the powerful endogenous vasoconstrictors that are released during stressful environmental conditions and, in turn, control their potential contribution to the development of NFCI.

Neural Considerations

In view of the cold-induced neuropathies consistently observed in NFCI, it would be of benefit to military medicine to attempt to develop prevention or therapy for maximal neuronal recovery. Among many current candidates for investigation, recent research has identified new neurotrophic factors related to the endogenous polypeptide, nerve growth factor, that have shown significant promise in promoting survival of damaged neurons that have been put at risk. Nerve growth factor and other related factors are members of a class of polypeptide neurotrophic factors that are involved in the development, survival, and maintenance of neuronal tissues. Consideration should be given to this class of factors, as nerve growth factor has been used successfully in treating a variety of neuropathies, including toxic drug-induced neuropathies due to taxol and cisplatin (two antitumor drugs) as well as diabetic neuropathy.[74,75] While not all neuropathies are alike, critical elements found in diabetic and drug-induced neuropathies may be similar to those found in NFCI-induced neuropathy. These similarities include impaired axonal transport, decreased sensory amplitudes, and modified thermal sensitivity. As NFCI shares many characteristics with these successfully treated neuropathies, it is possible that research with nerve growth factor may offer a viable means to prevent or ameliorate its associated neural dysfunction.

Nerve growth factor appears to be important in keeping neurons healthy and provides a first line of defense against environmental insult.[76] Critical to this function is the binding of nerve growth factor to receptors that promote phosphorylation of cellular proteins.[77,78] Nerve growth factor may play a vital role in ensuring that microtubules remain in proper assembled configuration for axonal transport, considered as a related dysfunction in NFCI, by interacting with microtubule-associated proteins. Nerve growth factor might also be potentially applicable to the prevention or treatment of NFCI because of its abilities to counteract the generation of free radicals that may occur during reperfusion and to maintain proper ion gradients across the cell membrane. As neurotrophic factors are intricately involved in the initial events of nerve regeneration, they appear to be a promising class of pharmacological agents for further consideration for potential treatment of NFCI.

PROTECTION AGAINST AND PREVENTION OF NONFREEZING COLD INJURY

Protection against exposure to cold, wet, stressful environments is surely the first step in preventing nonfreezing cold injuries. So simple a remedy is not necessarily possible during military campaigns, however, as constrictive clothing and lack of protective equipment, sleep, and nutritious food, combined with the tactical situation and a cold, wet, inhospitable environment, can predispose susceptible combatants to debilitating injury. Campaigns may have been lost before, and could be again, not because of enemy action but because of attrition from NFCI.

Protection Against Cold, Wet, and Stress

As prolonged exposure to cold, with or without concurrent wet or stressful environments, is an essential condition for induction of NFCI, it is obvious that any practice that limits exposure of an individual to the cold environment will reduce the probability of developing NFCI-or any other cold-induced injury.

Adequate thermal protective clothing is necessary for maintaining general body warmth, however, as it is the extremities that are most susceptible to NFCI; extra care must be taken to maintain local thermal protection, and in the more proximal sections of limbs through which arterial blood must flow to reach the distal extremities. As adequate maintenance of local blood flow is of prime importance in protecting against NFCI, protective gear should be not only of appropriate thermal insulation value but also nonconstrictive. This is particularly true for footwear, as constriction of blood flow in the feet certainly can hasten the development of NFCI. In this regard, it is also important that an individual remain mobile to ensure optimal circulation in the extremities.

There are extreme individual differences in the susceptibility to cold injury that are related to an individual's vascular reactions to the cold environment. Individuals capable of maintaining higher local blood flow and skin temperatures are often less susceptible to cold injury, given the same environmental conditions, than those with lower peripheral blood flow and skin temperatures. Consequently, great caution must be exercised when reexposing casualties who have had prior cold injuries, especially if there is any evidence that they suffer from residual cold sensitization.

The onset of NFCI can be hastened if individuals are malnourished and even moderately dehydrated while they are exposed to severe cold environments. Fatigue is also frequently a precipitating factor promoting onset of NFCI. Military personnel, especially commanders, should continually be aware of the ongoing physical stresses imposed by the surrounding terrain, particularly when it begins to induce a state of fatigue.

Finally, in consideration of factors that may promote the development of NFCI, medical officers should recognize that the stress associated with military operations and the vasoconstrictive effects that such stress induces—particularly stresses related to combat environments—seem to be among the more significant etiological factors. In this regard, it is important that education and training for troops to be deployed into cold operational environments recognize the constellation of precipitating factors that may lead to the onset of NFCI. Preventive education and training for military personnel will help preclude the onset of cold-induced injuries by making troops more aware of cold-related symptoms and the factors that are important in protecting against such problems. Medical personnel training for recognition of signs and symptoms of NFCI is important, as is doctrine relating to the care and rewarming of extremities. Medical personnel should be specifically targeted for intensive training in cold-related symptom identification and treatment.

EXHIBIT 15-2

A NEAR MISS IN THE FALKLANDS

The Falkland Islands are an isolated and bleak archipelago of peat and rock outcrops situated in the South Atlantic ocean between Tierra del Fuego, the stormy and cold extreme of South America, and the solitary near-Antarctic wilderness of South Georgia. Almost devoid of trees, roads, and human population, their climate is cold, wet, and windy; their weather ever-changing. As the British Task Force sailed south in 1982, planners back in the United Kingdom and medical officers embarked with the troops were only too aware that nonfreezing cold injury (NFCI) was likely to be a major problem.

Following the initial naval units, which secured sea access to the islands and engaged the Fuerza Aerea Argentina (Argentinian Air Force), the first wave of land forces consisted of three Royal Marines commando regiments and two Parachute battalions, all of whom were landed in a huge fjord-like inlet on 21 May 1982. The best-trained infantry units in the United Kingdom, many had only recently returned from arctic-warfare training in Norway, and all were considered to be highly experienced and well equipped, with high standards of fieldcraft. For many, the slippery slope to cold injury started on D day, when they became soaked to the waist as their landing craft were unable to reach dry land in the difficult beaches around San Carlos Water.

Once ashore, they discovered that digging defensive positions in the sodden peat only ensured that their feet would remain permanently wet. Whether they remained in those positions guarding the beachhead, or moved forward over the coming days as the advance built toward Stanley, most found that their footwear would not dry out again. They were using a wide variety of different boots: most had the traditional, short direct molded sole (DMS) model, of thin, lightly proofed leather (then the standard infantry boot of the United Kingdom); one commando had high-quality trial versions of its immediate successor, the combat high boot, which ran higher up the leg and was constructed to be more waterproof; others tried traditional reversed-grain leather mountaineering boots, which they had been using in Norway; there were also modern two-component plastic mountaineering boots, cross-country skiing boots, rubber Wellingtons, and more. Some wore a single pair of tough nylon socks, others two pairs of thick loopstitch "Arctic" socks, and clothing drawn from the full United Kingdom military range of the time, with many civilian enhancements.

By the second day after D day, casualties started to arrive at the 2nd- and 3rd-echelon medical support facility at Ajax Bay with a primary initial diagnosis of NFCI. All cases among United Kingdom troops were mild, with no overt tissue damage, but most were unable to sleep because of the pain, or to don their boots again because of the swelling. Most casualties had carried out routine foot care but had neither been resupplied with dry socks nor rotated into locations where they could dry out.

Although only 109 casualties reached 2nd- and 3rd-echelon medical support, they accounted for 14% of all British nonfatal casualties, and later examination of some of those returning to the United Kingdom revealed that 98% of the troops at the front line—the rifle or fighting companies—had suffered NFCI during the 4 weeks that they had been ashore. In contrast, incidence rates among logistical-support and rear-echelon personnel were almost 0%. Casualties with NFCI had clogged the evacuation chain, requiring scarce helicopters for their return to receive medical care. Once back there, they filled precious accommodation in the tiny settlements of the Falklands. Some were billeted on board logistical support vessels, and a few were further injured on board RFA *Sir Galahad* when she was hit off Fitzroy. Although they had not lost limbs or been otherwise mutilated by war, no more than a handful became fit enough to return to the frontline during the conflict.

The arrival of the Gurkhas, Scots, and Welsh Guards on 30 May 1982 still did not provide sufficient manpower for Divisional Command to start rotating troops. Concern grew that so many of those at the front line were unable to wear their boots, and that the steady trickle of cases becoming *hors de combat* was decimating field strength to the point that the final assault on Stanley could not be mounted. If the Argentine surrender had been delayed by several weeks, it is entirely possible that attrition of the British force due to NFCI would have been so great that a successful conclusion to the Falklands War would have been impossible. Among other factors, it was the operational cancer of NFCI that forced the pace toward the end of the conflict. Some 2,000 fit, well-trained, well-equipped infantry soldiers had succumbed to the same condition that had crippled their antecedents on the Somme in the fall of 1916. The poor bloody infantry had again rediscovered NFCI.

PREVENTION OF NONFREEZING COLD INJURIES IN MILITARY OPERATIONAL ENVIRONMENTS

At present, the most effective prevention of NFCI is simply to prevent prolonged exposure to cold. However, because of the complexities of military operations, and the confluence of factors that may lead to NFCI, such limitation to environmental exposure may be impossible to achieve. Additionally, operational considerations may preclude certain limitations on cold exposure. At the least, however, systematic rotation of personnel out of exposure environments or out of combat environments should be made a high priority in the planning of military operations. Undoubtedly, limitations on the duration of personnel exposure remain the main effective measure against NFCI.[4]

Efforts related to the development of protective equipment (such as vapor barrier boots) and concentrated training of personnel in hygienic foot procedures has helped reduce the incidence of NFCI.[4] However, footwear designed to eliminate the ingress of water can act as a double-edged sword by preventing the egress of liquid from the boot, where the latter is generated as sweat or results from leaks. Unless this moisture can be removed and dry socks donned, impervious footwear such as vapor barrier boots and vapor permeable layers worn within the boot can actually induce NFCI. The use of such highly protective assemblies therefore requires that wearers are able to carry out frequent foot-care routines and change into dry socks. These are often not possible. Related to foot hygiene are requirements that feet be kept warm and dry and not be allowed to remain motionless for lengthy periods. Constricting footwear, owing to its restrictive effects on blood flow within the foot, can also contribute to the development of NFCI.

Although strict adherence to these measures can be useful, in the realities of military operations and of combat in cold environments, application of comprehensive preventive measures has proven to be quite difficult, resulting in significant occurrence of cold injury.[79] For example, due to circumstances of combat, many of the British NFCI casualties in the Falkland War were Royal Marines who were arctic trained and maintained as high standards of foot care as were possible (Exhibit 15-2).[4]

Consequences of Nonfreezing Cold Injury as a Learned Disorder

An anecdotal account of the effects of military reassignment of patients with NFCI has suggested that cold sensitization, and possibly the other problems encountered in stage four, is extremely unusual in those who are sent to live in a tropical location soon after the end of stage three. Oakley[80] suggested that cold sensitization and other sequelae may be maladaptive responses in fundamentally normal neurovascular beds; coupled with that, he proposed that relocation to the tropics be made part of the formal treatment regime. There is already supporting evidence from a trial of conditioning[81] that this proposal is worth investigating. Even if it does not prove successful as a means of treating those with established NFCI, by preventing casualties from sustaining further damaging cold injury, it can only be beneficial.

SUMMARY

NFCI remains a significant medical problem in military operations performed in cold weather. When military operations must be carried out in cold and wet environments for more than a very limited time period, the probability is high that NFCI will occur. Practical operational considerations often do and will continue to preclude optimal prevention efforts based on limiting exposure of personnel. In more than half a century of research related to the occurrence of this injury in military environments, no other proven prevention strategies for NFCI have been found.

Over the past decades our understanding of the mechanisms and systems associated with the pathophysiology of vascular damage, neural dysfunction, combat stress, and reperfusion injury has been greatly enhanced through research in areas not directly related to cold-induced injuries. However, medical research focused on the sequential progression of events involved in cold-induced modulation of those mechanisms and systems is lacking. To safeguard the health, safety, and ability of military personnel to successfully complete their missions while working in cold environments, it is imperative that more attention be focused on elucidating pharmacological and physiological strategies for breaking the core of the vicious circle of peripheral cooling, prolonged sympathetic tone, and cold-induced vasoconstriction. It is also crucial that we identify effective treatment regimens for casualties that occur when prevention efforts fail, particularly for the problems of cold sensitization and residual pain.

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