Contribution of Dr. William J. Mills

to the treatment of frostbite

By

Maryam Gharraei Khosroshahi

A Thesis submitted to The Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Faculty of Kinesiology and Recreation Management

University of Manitoba

Winnipeg

Table of Contents

ACKNOWLEDGEMENTS

I thank my advisor, Dr. Gordon Giesbrecht, for his instruction and help in this study. I like to thank my committee members Dr. Ken Zafren and Dr. Rodrigo Villar for their recommendations on this project.

I would like to express my deepest gratitude to my family for supporting me throughout my education.

DEDICATION

To my father and teacher who provided me endless love and support.

He passed away March 2022.

ABSTRACT

Dr. William J Mills Jr., an Alaskan orthopedic surgeon, helped establish the protocol for the treatment of frostbite and changed a dogma used for more than 140 years that was offered by Napoleon's Surgeon General of the Army, Baron Dominique-Jean Larrey. During Napoleon's 1812 siege of Moscow, in which one of the most disastrous frostbite epidemics happened, Larrey noticed the destructive effects of using open fire heat for warming frozen body parts, so he suggested rubbing snow or immersion in the cold water. Dr. Mills had an interest in cold injuries and frostbite during his medical career. After setting up his medical practice in Anchorage, Alaska, he realized the inefficiency of current treatments and started researching treatment of frostbite. Dr Mills followed Meryman's method of thawing frozen red blood cells by immersion in warm water. Mills and his colleagues established a treatment protocol for freezing cold injury that included rapid warming of frozen tissues in warm water. These studies resulted in publication of three papers in 1960 and 1961. These papers were the first clinical studies which described rapid warming as a treatment. Subsequently, rapid warming, with some variation in water temperatures, has been accepted as the standard of treatment universally. Due to his outstanding contribution to the treatment of frostbite, he has been referred to as North America's leading authority on cold injuries. Mills and his colleagues created a new classification system which divided frostbite into two levels, superficial and deep, which was more applicable in clinics instead of traditional 4-tier classification. The 2-tier classification is still useful outside of the hospital setting.

CHAPTER 1: INTRODUCTION

William J. Mills, Jr, an orthopedic surgeon in Anchorage, Alaska, is well known for his research on hypothermia and frostbite. He obtained his medical degree from Stanford Medical School in 1949 and completed his orthopedic residency at the University of Michigan. He began to see frostbite cases very soon after he established his practice in Anchorage in 1955. He realized that while many treatments were available for frostbite, none of them had much success and some even caused additional harms. Limb amputation in frostbite cases stimulated him and his colleague Dr. Robert Whaley to improve treatment methods [1].

In 1960 and 1961, Mills and his colleagues published three papers in series on the treatment of frostbite that was fundamentally responsible for a paradigm shift in the treatment of frostbite [2-4].

Frostbite is defined as tissue damage that occurs when tissues are exposed to temperatures below 0°C, long enough to initiate ice crystal formation in the affected tissue [5]. Crystals form when tissue temperature is below -4ºC and ambient temperatures (or wind chill equivalents) are usually less than -30°C.

Cost and hospitalizations after frostbite injury (for admissions and readmissions) were investigated in Nationwide Readmission Database in the United State since 2016 [6]. During a 2-year period (2016 and 2017), 1065 index hospitalizations and 842 readmissions resulted in total 1907 hospitalizations following frostbite injury. The estimated rate for unplanned readmission was 35% following frostbite injury. 29% of freezing injuries resulted in at least one amputation. The estimated cost for each index frostbite admission was $23,000and average stay

at the hospital was 12 days. The cost and average stay at the hospital for the first unplanned readmission was $23,000 and 12.3 days [6].

A 12-year study into inpatient frostbite injuries in the northern prairies of Saskatchewan reported alcohol consumption, psychiatric illness, vehicular trauma, vehicular failure, and drug use as the predisposing factors in frostbite cases. Based on this study, alcohol consumption was the leading (46%), and most devastating, factor. Alcohol impairs judgment causing irrational decisions that increase the risk of frostbite, like taking off their cloths or not to seek appropriate protection (shelter) from cold. Alcohol may increase skin temperature through peripheral vasodilatation but this effect is temporary and very soon the signals going through receptors to the central nervous system result in permanent vasoconstriction [7].

The pathophysiology of frostbite has been described by a progression through four overlapping phases: 1) pre-freeze phase; 2) freeze-thaw phase; 3) vascular stasis phase; and 4) late ischemic phase [8]. Cell injury and vessel damage are responsible mechanisms for pathological changes during freezing [9].

Cellular injury occurs when intracellular or extracellular ice crystals form. Ice crystals form preferentially in the extracellular spaces during freezing except at very high rates of freezing when intracellular crystals form predominately. The formation of crystals in extracellular spaces creates a hypertonic solution outside the cell so the intracellular water passes through the membrane to the extracellular space. This process causes cell dehydration and a high concentration of electrolytes, sugars, proteins, and enzymes which result in accumulated injury and cell lysis [10].

The initial vascular response is decreased blood flow after vasoconstriction at the first exposure to the cold and ends in showers of emboli in microvessels at the last ischemic phase [11]. Sub-zero temperatures damage microvascular endothelium directly so platelets and other blood cells attach to the damaged wall. Microvascular damage not only accelerates local transcapillary plasma loss and edema formation, but also promotes the formation of microthrombi, which occlude capillaries and lead to ischemia. Microvascular clots form during freezing and thawing stages, however it is not clear in which stage this is dominant. Ischemia is an outcome of several factors which positively augment each other. These factors include intravascular sludging, endothelial damage, increased inflammatory mediators and free radicals, reperfusion injury, and thrombosis [12] [13].

Frostbite injury has historically been classified into four degrees: 1) first degree frostbite is characterized as reversible superficial changes; 2) second-degree frostbite is superficial dermal damage; 3) third-degree frostbite is indicated by deep dermal injury; and 4) fourth-degree frostbite causes damage to subcutaneous tissue, muscle, nerves, and/or bone [14].

Because of difficulty of determining the four degrees of freezing in the field, Dr Mills offered an alternate 2-tiered classification that is now commonly applied in out of the hospital setting: superficial injury with minimal, or no, anticipated tissue loss (corresponding to first- and second-degree frostbite); and deep injury with anticipated tissue loss (corresponding to third and fourth-degree frostbite) [3].

Napoleon’s chief surgeon, Baron Dominique Jean Larrey gave the earliest description of the pathophysiology of frostbite during the French army’s retreat from Moscow in the winter of 1812–1813 [15]. Larrey's observations of the effects of rapid rewarming near excessive fire heat

convinced him that very slow rewarming would cause less pain and tissue damage, thus he introduced the concept of friction massage with ice or snow [16] [17].

Rubbing a frozen limb with snow remained the accepted treatment for frostbite until World War I, and even later. In the 1930s, Ariev from the Medical Academy of the Union of Soviet Socialist Republics (USSR) Army, through experiments on rabbits, demonstrated that rapid rewarming by immersing the frozen part in warm water was better than the previous methods [18]. Ariev originally published his research in Russian in 1940, but western physicians were not aware of these studies until Iser Steiman, from the Canadian Department of Defense, translated these papers into English following World War II in 1955.

In 1960-1961, Mills and his colleagues published three papers in Alaska Medicine and explained their experience with human cases treated by different methods. In this research, they compared the outcomes of different modalities of treatment with their method and demonstrated that rapid warming in warm water is the best method for treatment of frostbite [2-4].

These three papers were the first clinical reports from the West to introduce rapid warming treatment, and they impacted the treatment of frostbite in subsequent years. Rapid warming (with variations in water temperature), became the most desirable method of treatment in the world [1].

Dr Mills for more than forty years treated, or consulted on, more than 1500 cold injury cases including more than 1000 frostbite cases [8]. He continued researching the treatment of frostbite and cold injuries and improved his method over time and provided a protocol for field and hospital treatment of frostbite.

The purpose of this study is to search for all of Dr. Mills' papers and select and summarize the papers which relate to frostbite. The secondary purpose is to analyze his contributions to frostbite treatment.

CHAPTER 2: LITERATURE REVIEW

BIOGRAPHY

Dr. Mills was born in San Francisco in 1918. He graduated from High School in Riverside, California, in 1936. He left home to attend the University of California at Berkeley where he said he "majored in Anthropology, Zoology, and Poverty" [19]. After graduating from the university, he enlisted in the Navy as an apprentice seaman when Pearl Harbor was attacked. He enlisted in the Navy and served as the commander of PT 181 in the U.S. Navy during World War II from 1942 to1945. Mills sustained two open fractures of both his lower legs during the Solomon Islands Campaign. Due to the hard conditions on Kolombangara Island at the time, there was no access to proper health care and one of his legs was amputated because of gangrene [19].

He received his medical degree from Stanford University Medical School in 1950. He then began a residency program in orthopedic surgery at the University of Michigan. After finishing his residency, he went on to a Fellowship at Vanderbilt University in Tennessee under a United Cerebral Palsy Grant [20]. In 1955 Dr. Mills started an orthopedic practice in Anchorage, Alaska and the following year he was voted Alaskan Physician of the Year. He was a founding member of the Alaska State Medical Association and the first Editor and Chief of the journal "Alaska Medicine". Dr. Mills continued serving in the Naval Medical Corps Reserve from 1956 to 1978 and retired as a Rear Admiral. from 1966 -1967, he also served as Chief of Orthopedic Surgery for the III Marine Amphibious Force in Vietnam [20].

During his practice in Anchorage, he started seeing frostbite cases which significantly increased due to the replacement of dog teams by snow machines. While dogs could save the

person by bringing them home, snow machines were susceptible to failure [19]. The increasing number of frostbite cases, the lack of effective treatment, and the loss of limbs due to freezing motivated Dr. Mills to investigate the treatment for this injury [1].

In 1960 and 1961, Mills and his colleagues published three papers in Alaska Medicine and proposed a method of treatment for frostbite, which changed the current treatment of frostbite at that time in most of the world [2-4].

In the 1980s, Dr. Mills directed altitude research on Denali at 14,000 feet with the support of a grant from the State of Alaska for the High Latitude Research Project. This project was terminated due to the withdrawal of military logistical support during the first Gulf War [19]. Dr. Mills was cited as "the nation's leading authority on cold injury" at the Mountain Medicine Lecture Series at the University of California in the 1980s [20].

Dr. Mills served as Emergency Medical Services (EMS) Medical Director for the State of Alaska; however, prior to the establishment of the paid position, he served this role voluntarily. He later served as a consultant for Emergency Medical Services and had an active role in writing the State of Alaska Cold Injury Guidelines through numerous revisions from 1982 to 2005, the last version he participated in [19].

Dr. Mills received several awards through his lifetime including from the Mayor of Anchorage; Anchorage School District; Alaska Area Native Health Service; National Aeronautics and Space Administration (NASA); American Medical Association and the Jack Hildes award from The American Society for Circumpolar Health; also he received a medal from the City of Lecco, Italy for his help with their Mt. McKinley climbing team [20]. In 2001, he was awarded the Distinguished Achievement Medal from the University of Michigan Medical

School. Dr. Mills was awarded an honorary doctorate by the University of Alaska Anchorage and the University of Manitoba. William J. Mills, Jr passed away on December 4, 2011, at age 93.

Besides his medical professional career, Dr. Mills was a professional photographer and many of his photographs of birds were published on the cover of "Alaska Medicine." [20].

“Bill’s legacy is not just in revolutionizing the treatment of frostbite. Thousands of patients benefited from his orthopedic care. Medical professionals at all levels of training as well as members of the public benefited from his efforts to educate everyone about the prevention and treatment of cold injuries. Many, like the author, were fortunate to benefit from his personal mentorship” [19].

FROSTBITE DEFINITION

Frostbite is defined as tissue damage happening when ice crystals form in the tissue. It is a cold injury that commonly occurs locally in the extremities or facial organs such as the ear or nose [21]. The location of ice crystal formation depends on the rate of freezing. When this rate is very fast, ice crystals form in the intracellular space, otherwise ice crystals commonly form in extracellular water [10]. Thrombosis, ischemia, gangrene and ultimately amputation can happen depending on the degree of tissue damage. The most affected parts of the body are the fingers, toes, nose, ears and cheeks [5].

EPIDEMIOLOGY

Historically, frostbite was primarily a problem in military operations however, recently, concern over frostbite has become broader [22]. The growing number of homeless people, along with increased participation in outdoor activities and sports in harsh environments have been responsible for the increase in the incidence of frostbite in the civilian population.

An epidemiologic review of the first 10 years of the Everest ER, the Himalayan Rescue Association clinic at Everest Base Camp in Nepal, reported that cold exposure accounted for 18% of all trauma visits [23]. Cold injuries consisted of frostbite (84%), frostnip (11%), and non-freezing cold injuries (5%). A 10-year retrospective study from the National Park Service (in Alaska) medical reports from Denali (Mt. McKinley) climbers found frostbite to be the most common individual diagnosis (18%) [24].

RISK FACTORS

"Air temperature, wind speed, duration of exposure, amount of exposed area, and some predisposing conditions can affect the severity of frostbite. Predisposing conditions include poor or inadequate insulation from the cold or wind; immersion; altitude; impaired circulation from tight clothing or shoes; fatigue; injuries; circulatory disease; poor nutrition; dehydration; hypothermia; alcohol or drug use; and use of tobacco products" [25].

Based on many publications on frostbite among civilians, frostbite victims can be divided into two groups [14]. The first group includes people who had cognitive alteration during exposure to freezing due to alcohol, drugs, or psychiatric problems. The majority of these

patients are young males between 30-49 years of age. Even though alcohol is a vasodilator and would theoretically warm fingers, and decrease the risk of frostbite, it decreases awareness. These victims often do not seek appropriate shelter [26]. The second group includes people who were injured in vehicular trauma (accident or failure), extreme winter sports, mountaineers, and those working outside in the extreme cold with metal tools.

PATHOPHYSIOLOGY OF FROSTBITE

A detailed description of the progression of tissue freezing includes four phases: 1) pre-freeze; 2) freeze-thaw; 3) vascular stasis; and 4) progressive or late ischaemic [27] (Table 1). Mills simplified progression of freezing into two phases: 1) the cooling, supercooling, freezing phase; and 2) the thawing (rewarming) and post-thaw phase [8].

Table 1. Different systems to describe frostbite classifications and pathology.

<table>
<tr><td></td><td>Traditional systems</td><td>Mills systems</td><td>Cauchy system</td></tr>
<tr><td rowspan="5">Classification</td><td>Frostnip</td><td colspan="2"></td></tr>
<tr><td>1st degree (partial skin freeze, no blisters)</td><td rowspan="2">Superficial (1st and 2nd degree)</td><td>Grade 1 (no blisters)</td></tr>
<tr><td>2nd degree (full skin freeze, clear blisters)</td><td>Grade 2 (freeze distal phalanx, clear blisters)</td></tr>
<tr><td>3rd degree (freeze of skin and subcutaneous tissue, hemorrhagic blisters)</td><td rowspan="2">Deep (3rd and 4th degree)</td><td>Grade 3 (freeze mid and proximal phalanx, hemorrhagic blisters)</td></tr>
<tr><td>4th degree (freeze deep tissue including bone, hemorrhagic blisters)</td><td>Grade 4 (freeze carpal/tarsal, hemorrhagic blisters)</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td rowspan="4">Pathology</td><td>Phase 1 (pre-freeze)</td><td rowspan="2">Stage 1 (cooling, supercooling, freezing)</td><td rowspan="4"></td></tr>
<tr><td>Phase 2 (freeze-thaw)</td></tr>
<tr><td>Phase 3 (vascular stasis)</td><td rowspan="2">Stage 2 (thawing and post-thaw)</td></tr>
<tr><td>Phase 4 (progressive or late ischemia)</td></tr>
</table>

Phase 1. Pre-freeze

In the pre-freeze phase, tissue cooling initiates vasoconstriction and ischemia without ice crystal formation. Ischemia and neural cooling cause hyperesthesia or paresthesia [10]. Skin cooling, whether in cold air or water, initially produces sensations of cold and then pain. Cold causes vasoconstriction, and decreased blood flow causes further skin cooling. The skin becomes numb at or below 10°C and it loses sensation of fine touch and ultimately all touch sense as sink temperature approaches 0°C [28]. However, after 5 to 20 minutes, temporary and cyclic vasodilation occurs and skin temperature in the digits increases [29]. This may result in severe pain. cold-induced vasodilation (CIVD) is often referred as Lewis's hunting response or Hunting response [30]. Finally, cold blood returning from venules to the central nervous system cause vasoconstriction which is persistent.

Phase 2. Freeze-thaw

When tissue is cold enough ice crystals commonly form in extracellular water, unless freezing is very fast, crystals predominately form intracellularly. This is not common in clinical cases [10]. When crystals form in extracellular space this produces a hypertonic solution outside the cell so the intracellular water passes through the membrane to the extracellular space and adds to ice crystals. The extraction of intracellular water produces a high concentration of electrolytes, sugars, and proteins in these cells. Some structural damage is possible from ice crystal growth, however chemical damage is the prime cause of cell injury rather than mechanical destruction [10].

As freezing continues, there is intracellular and extracellular dehydration, extra- and intracellular electrolyte and pH changes, destruction of enzymes, and possible direct mechanical and non-mechanical damage to the cell membrane [8]. Marzella and his colleagues reported

endothelial cells separating from internal elastic lamina immediately after freezing and they noticed severe damage to the cartilage [31]. Degenerative changes in muscle and connective tissue have been reported within 15 minutes after freezing. This injury was not because of stasis and thrombosis, rather it was a direct effect of freezing [32].

The usual events after thawing are vasodilation, edema, and stasis. There is vasoconstriction at the time of freezing which is indicated by the whitish appearance of the frozen part [33]. This vasoconstriction is replaced by vasodilation after thawing as evidenced by the redness and warmth of the affected part. When thawing is accomplished and circulation resumed, plasma leaks from vessels and the swelling starts. This indicates that damage occurs soon after resuming circulation. The thawing process may result in reperfusion injury, inflammatory response and ischemia [10].

The severity of cellular damage depends on the final freezing temperature, duration of exposure to freezing temperature, and the rate of cooling. In addition, the method of warming of the frozen tissue affects the degree of cell destruction in the thawing phase. Long duration of thawing results in more damage, see below [34].

Phase 3. Vascular stasis

Platelets and other cell elements attach to the vessel walls immediately after thawing because of the damage of freezing to the microvasculature [11]. The damaged walls of vessels due to increased permeability allows the plasma to escape into the tissues leaving the blood cells concentrated in the vessels. Very soon, from 5 to 10 minutes after thawing, blood flow starts to diminish in injured tissue [33]. Within 10 minutes after thawing, swelling, intravascular aggregation of platelets and separation of endothelial cells occurs. Within one hour, leukocyte

influx and stasis, and detached endothelial cells in the lumen in venules and arterioles have been detected [31].

In addition to structural changes in vascular endothelium that result in vascular permeability alteration and platelet aggregation, the release of chemical mediators from endothelial cells, platelets, and mast cells modulates vascular contractility, permeability, aggregation [31]. Robson and Heggers reported that the vasodilating and platelet anti aggregating substance, prostaglandin E2 was diminished, whereas, the vasoconstricting and platelet aggregating substances, prostaglandin F2α and thromboxane B2 were significantly increased in the frostbite blisters[35].

Phase 4. Late ischemia

Zacarian and his colleagues documented that within a few minutes after thawing, some emboli adhered to vessels momentarily and then detached being carried through the blood vessels. When blood flow was fast enough, they detached by blood flow and carried it along the vessels. However, when the rate of blood flow decreased platelet thrombi and white thrombi attached to the vessel endothelium, and finally, they adhered permanently and occluded the vessels. After a while, showers of emboli were passing through venules. Eventually thrombosis developed in macrovesicles and circulation arrest occurred persisting throughout 24 h [11].

Progressive tissue ischemia and infarction occur due to a cascade of events including inflammation, mediated by prostaglandin F2α, thromboxane A2, bradykinin, and histamine; intermittent vasoconstriction of arterioles and venules; reperfusion injury; and showers of emboli in the micro vessels occur in the late ischemic phase [8].

Refreezing

During slow freezing, ice crystals generally form in the extracellular spaces, while refreezing after thawing produces uniform ice crystals intracellularly, which can damage the cell membrane or intracellular organs such as the mitochondria [36]. This cycle is destructive for cells and usually lethal to the affected tissue.

CLINICAL CLASSIFICATION OF FROSTBITE

There have been several classification systems for frostbite. The traditional classification for frostbite divided frostbite into frostnip, first-degree, second-degree, third-degree, and fourth-degree depending on the depth of injury [12] (Table 1).

Old classification

Frostnip

Frostnip is a non-freezing cold injury that can proceed to frostbite. In the frostnip stage, ice crystals do not form in the tissue; however, skin is white and numb. After rewarming, it becomes hyperemic and paresthetic. Paresthesia (burning or prickling sensation) can be prolonged for weeks, but recovery is complete [21].

First degree

Skin is frozen partially, and the frozen tissue is numb and erythematous. Edema is common, but it is minor. There is no blistering, however a white or yellow plaque forms in the injured area. There is no necrosis or tissue loss [37].

Second degree

Full thickness of the skin is frozen. The tissue has substantial edema and erythema. Distal blister formation occurs within 6 to 24 hours, and the fluid is clear.

Third degree

Freezing of the skin and subcutaneous tissue occurs. The tissue is blue or black. Patients have deeper, proximal, hemorrhagic blisters and necrosis.

Fourth degree

Freezing of the skin, subcutaneous tissue, muscle, tendon, and bone occurs at this level. The tissue is Initially deep red and mottled and eventually changes to black and mummified. There are few or no blisters. There is profound necrosis [13] [37].

Because the bone loss is always distal to frostbite lesion, this classification could not give a precise prediction about the eventual amputation level, which is always apparent after mummification in subsequent days. Over recent years, there has been an effort to achieve more prognostic rather than observational classifications [12].

Dr. Mills and his colleagues offered a simplified classification for frostbite injury because of the difficulty of distinguishing the various degree of frozen tissue clinically. They categorized frostbite injury into two levels; superficial and deep. Superficial frostbite corresponds to the first and second degree in the traditional four-degree classification in which the freezing injury is limited to the skin. Deep frostbite refers to destruction in tissues beneath the skin including muscles, tendons, nerves, blood vessels, and bone which corresponds to the third and fourth degree in the traditional four-degree classification. [3].

New classification

Cauchy and colleagues suggested a prognostic classification system based mainly on the appearance of the lesions on day 0 and based on early bone scan results on day 2 [38]. They classified frostbite injuries with 5 levels of involvement (e.g., from distal phalanx to carpal/tarsal) based on the initial lesions on day 0 by using a retrospective study of the clinical records of 70 patients hospitalized for severe frostbite injuries of the extremities and studying their initial injuries and their final outcomes (Table 2). They also proposed a 4-grade classification after thawing on day 2 by using the results of early bone scan [39] (Table 3).

Table 2: Amputation based on initial lesion [38].

	Level of involvement	**Probability of bone amputation (95% CI)**
Hand	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	100
	3 (proximal phalanx)	83 (66;100)
	2 (intermediary phalanx)	39 (25; 52)
	1 (distal phalanx)	1 (00; 03)
Foot	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	98 (93; 100)
	3 (proximal phalanx)	60 (45; 74)
	2 (intermediary phalanx)	23 (10; 35)
	1 (distal phalanx)	0
Hand and foot	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	98 (95; 100)
	3 (proximal phalanx)	67 (55; 79)
	2 (intermediary phalanx)	31 (22; 41)
	1 (distal phalanx)	1 (00; 02)

Table 3: Classification for severity of frostbite injuries [38].

Frostbite injuries of extremities	Grade 1	Grade 2	Grade 3	Grade 4
Extend of initial lesion at day 0 after rapid rewarming	Absence of initial lesion	Initial lesion on distal phalanx	Initial lesion on intermediary (and) proximal phalanx	Initial lesion on carpal/tarsal
Bone scanning at day 2	Useless	Hypo-fixation of radiotracer uptake area	Absence of radiotracer uptake area on the digit	Absence of radiotracer uptake area on the carpal/tarsal
Blisters at day 2	Absence of blisters	Clear blisters	Hemorrhagic blisters on the digit	Hemorrhagic blisters over carpal/tarsal
Prognosis at day 2	No amputation	Tissue amputation	Bone amputation of digit	Bone amputation of the limb ±Systemic involvement ±Sepsis
	No sequelae	Fingernail sequelae	Functional sequelae	Functional sequelae

HISTORICAL PERSPECTIVE

Baron Dominique-Jean Larrey

Historical records have documented cold injuries, including frostbite and hypothermia, as important causes of mortality and morbidity. The first physical evidence of freezing injury is in a 5000-year-old mummy discovered in the Andes [12]. One of the earliest large-scale reports is from Hannibal crossing the Alps in 218 BC when only 19,000 survived from 38,000 soldiers; most deaths occurred due to hypothermia.

One of the largest series of frostbite cases occurred during Napoleon's 1812 siege of Moscow, and the subsequent disastrous retreat in the Russian winter. Napoleon's Surgeon General of the army, Baron Dominique-Jean Larrey had the opportunity to observe thousands of

victims of frostbite and the destructive effects of freezing [17]. He also noticed the disastrous effects of using a campfire for warming the frozen part and wrote "Persons were seen to fall dead at the fires of the bivouacs those who approached the fires sufficiently near to warm frozen feet and hands were attacked by gangrene in all points, where the vital powers had been reduced" [15].

After this observation Larrey proposed a method for treatment of frostbite: "it will easily be convinced after what I have just said why in the mortification of some external part of the body caused a cold, instead of submitting it to heat, which provokes gangrene, it is necessary to rub the affected part with a substance containing very little caloric, but which may absorb a good deal at the moment of their melting and transmit it to the frozen part by rubbing" [15].

Larrey also offered an alternative treatment: "should these remedies fail [e.g., rubbing the affected part with snow], the part ought to be plunged in cold water, in which it should be bathed. This is the process, adopted by the Russians, for thawing a fish. If they soak it in warm water, they know from experience, that it will become putrid in a few minutes; whereas, after immersion in cold water, it is as fresh as if it had just been caught" [15].

Larrey's contributions to military surgery and his perceptive observation of frostbite pathogenesis along with his analytical approach to the trauma made him a very prominent surgeon. Larrey's recommended treatment for frostbite due to the authority of his position and his significant experiences became the standard treatment for frostbite for more than a hundred years [40].

During World War I and between the two World Wars (1918-1939), rubbing with snow or immersion in a cold bath were almost universally the recommended treatments for frostbite.

Rapid rewarming was contraindicated because of producing more pain, swelling than slow rewarming [40].

T.J. Ariev

In the 1930s, Professor T.J. Ariev challenged the slow warming method for frostbite. He gave a summary of previous scientists who accepted slow rewarming and stated there was not any concrete clinical evidence that demonstrates the harmful effect of rapid warming. Ariev declared the experiments used to prove the positive effects of slow warming were insufficient and the principle of slow warming was not based on clinical fact. Ariev and his collogues, working at the Kirov Medical Academy of the USSR Army, carried out several experiments to investigate the effects of rapid warming.

Ariev and his colleagues published several papers but initially they were not translated to English. Thus, western physicians were not aware of these studies until these papers were translated into English by Dr. Iser Steiman of the Canadian Department of Defense during World War II [18].

Ariev warmed frozen rabbits' ears and extremities in two different conditions to compare the results of rapid warming (warm moist compress 35-40°C) with slow warming (thawed in the air). Rapid warming produced a significant decrease in the zone of necrosis in comparison to slow warming [18] . After several experiments Ariev proposed rapid warming for frostbite: "By the term 'rapid warming' we mean warming carried out by means of warm water baths of 30 - 35.5°C. It should not be considered that rapid warming in frostbite has specific curative advantages. The less marked degenerative changes and necrosis observed during rapid warming of frozen extremities should be entirely explained by a decrease in time of action of low tissue temperature" [18].

Harold Meryman

"Meryman, a US Navy medical office, became one of the world's leading investigators in cold-related science and cryobiology" [8]. He contributed to cryobiology in many aspects including the description of the extracellular ice formation and subsequent cell injury, extracellular solute concentration effects, and the methods of ice-crystal nucleation. He provided a precise description of the effect of the rate of freezing (slow or rapid) on biological systems of cells during the years 1955 to 1957[8].

One of his exceptional articles which affected subsequent research was the paper that he published in 1956 about the cryopreservation of living cells. Meryman explained the practical application of freezing for the preservation of living cells and offered three rules for this goal: I) very rapid freezing; II) low-temperature storage; and III) very rapid thawing [41].

William J. Mills Jr.

The 1950s and 1960s were a special era in frostbite research. The possibility of war against the USSR motivated the US defense organization to invest in research about frostbite which resulted in reports on the physiology, pathology, and treatment of frostbite. Mills who had a keen interest in cold injuries, received a grant from the Office of Naval Research Department to investigate frostbite [1].

Dr. Mills utilized Dr. Harold Meryman's research especially the project of cryopreservation of living cells at the US Naval Research Lab, and later at the American Red Cross, and applied rapid warming for the treatment of frostbite [41].

In a series of papers in 1960-1961, Dr. Mills and his colleagues published the results of treatment of 51 frostbite cases to compare the results of a variety of treatments. They

recommended that the frozen part be rewarmed rapidly in warm water at temperatures of 42 to 48°C, which changed the current standard treatment in the west and most of the world [2].

Dr. Mills' contribution to freezing injury besides popularizing this method for frostbite treatment includes offering a new classification for clinical application. His proposed classification changed the traditional four-tier classification to a simpler two-tier classification (e.g., superficial and deep). That was more practical for clinical use and is currently used in the field [3].

Dr. Mills coined the term, metabolic icebox: "the victim in this condition as in a mid-lethal state, so that further exposure would result in death, as cooling of vital organs continued without intervention and warming. Warming in this state, however, if not controlled physiologically, would often result in death because of uncorrected acid–base and electrolyte imbalance, usually acidosis, with hypovolemia and dehydration. Warming of the hypothermic victim, when freezing cold injury is also present, may release potassium from increased cell permeability or cell destruction. The often-sudden, high-level hyperkalemia may result in cardiac arrest and death" [8].

CHAPTER 3: METHODS

This research provides a narrative review of publications of Dr. William Mills to investigate his contribution to the treatment of frostbite and give a comprehensive summary of his publications in related areas. This study was conducted in three different sections to evaluate Dr. Mills' achievements (Figure 1).

MEDLINE DATABASES SEARCH

The first section included a Medline search for all his publications and summarized as annotated bibliography. The Medline database was searched for all publications of William J Mills. References for these publications were exported to the Rayyan QCRI program for the determination of eligible papers for analysis.

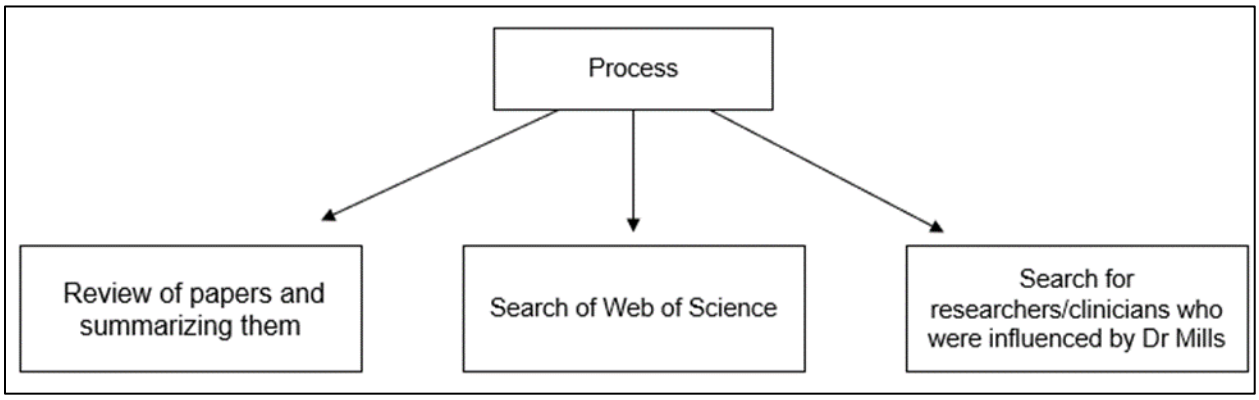

Figure 1: Three sections of this review.

In Rayyan, inclusion and exclusion criteria were applied. Inclusion criteria consisted of articles related to frostbite, hypothermia, and cold injury. Exclusion criteria included articles in

orthopedics, high altitude, or not related to frostbite, hypothermia, and cold injury. Two reviewers then independently (blinded) screened all articles and chose those that met the inclusion criteria; for each article, a choice was made to include, exclude, or maybe. Results of the screening were unblinded to determine the degree of agreement between the two reviewers.

All papers on cold injury were reviewed and categorized into four different areas based on their subjects: frostbite, frostbite and hypothermia, hypothermia, and immersion or non-freezing cold injury (NFCI). Every article was summarized in an annotated bibliography format. This summary included the paper main points, authors' names, date of publication, and journal information.

SEARCH OF WEB OF SCIENCE

The second section was the search of Web of Science to get the H-index and citation numbers for his papers and get information about citations in guidelines, textbooks and the contribution of Mills as a senior author or coauthor. The search was done on the Web of Science for Dr. Mills' publications. These papers were about several subjects including frostbite, hypothermia, immersion, high altitude, and orthopedics. H-index and citation numbers for all papers were reported. Since the citation and information about particular papers (frostbite, hypothermia, and immersion (NFCI)) were important for this study, the data for these papers were obtained separately from the Web of Science.

We divided the papers based on their subjects into four groups: frostbite, hypothermia, frostbite and hypothermia, and immersion injury (NFCI) (the same categories were used in the review of papers). The citation history was reported for all papers then the history was reviewed

for each individual paper to find out citations in guidelines and textbooks and to find out the number of citations on every subject. we also determined the number of papers in which Dr. Mills was the senior or sole author, or coauthor.

SEARCH FOR RESEARCHERS WHO WERE INFLUENCED BY DR. MILLS

The third section included a search for researchers or clinicians who were influenced by Dr. Mills. We made an effort to find the researchers or clinicians who were influenced by Dr. Mills. Therefore, we investigated some coauthors whose names were in Dr. Mills' publications.

CHAPTER 4: RESULTS

RESULTS FEROM SEARCH PROCESS

Following the Medline search, the agreement during the Rayyan analysis was 100% (Table 4 indicates that the Kappa value was 1.0). Twenty-five papers met the inclusion criteria. Sixty papers were not included because either: they were not related to cold injuries; they were from a different author with the same name; or they were about orthopedics, high altitude, or other non-related subjects (Figure 2).

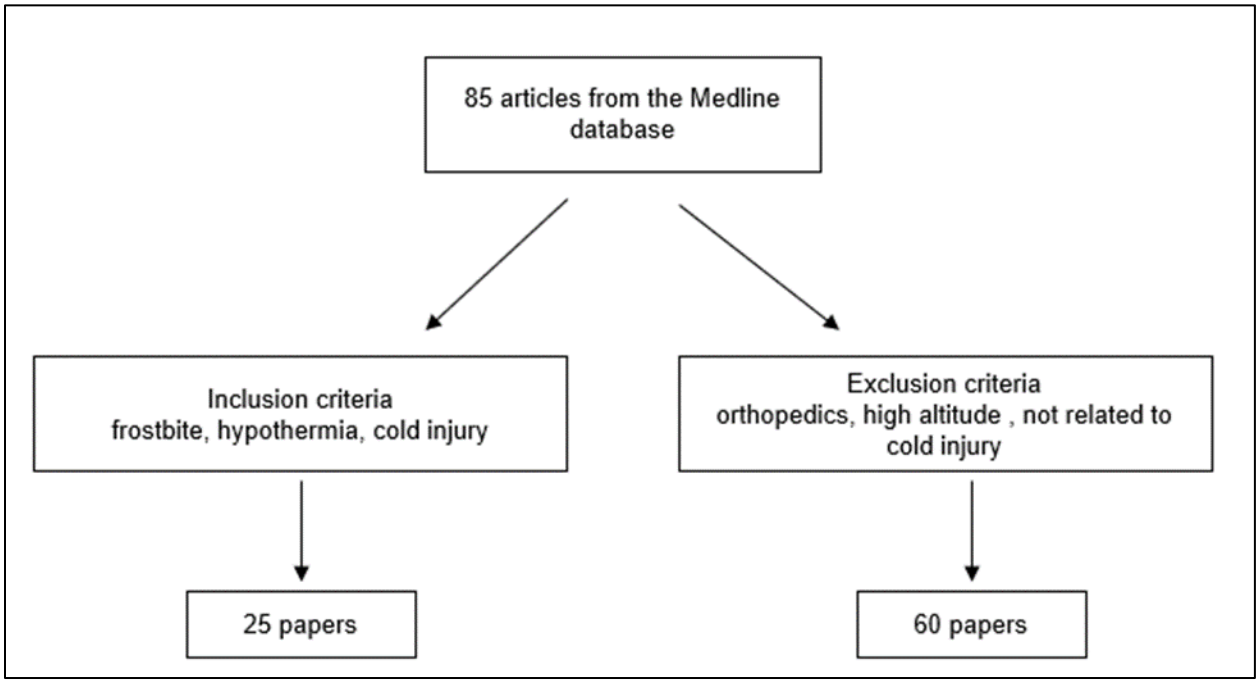

Figure 2: Selection process of papers

Table 4: KAPPA calculation

	A	B	C	D	E	F
1	**COHEN's KAPPA STATISTIC CALCULATOR**					
2			Gord			
3			**No**	**Yes**	**Total**	
4	Maryam	**No**	60	0	60	
5		**Yes**	0	25	25	
6		**Total**	60	25	85	
7						
8						
9	Observed Agreement			100%		
10	Chance Agreement			58%		
11	Kappa			1		

A search was also done in the University of Alaska (Anchorage) medical library for Dr. Mills' publications. All articles had already been obtained from the Medline database except one conference paper that was added to our papers and the number of papers became 26. We categorized all cold injury papers into four different areas based on their subjects: frostbite, frostbite and hypothermia, hypothermia, and immersion or non-freezing cold injury (NFCI) (Figure 3).

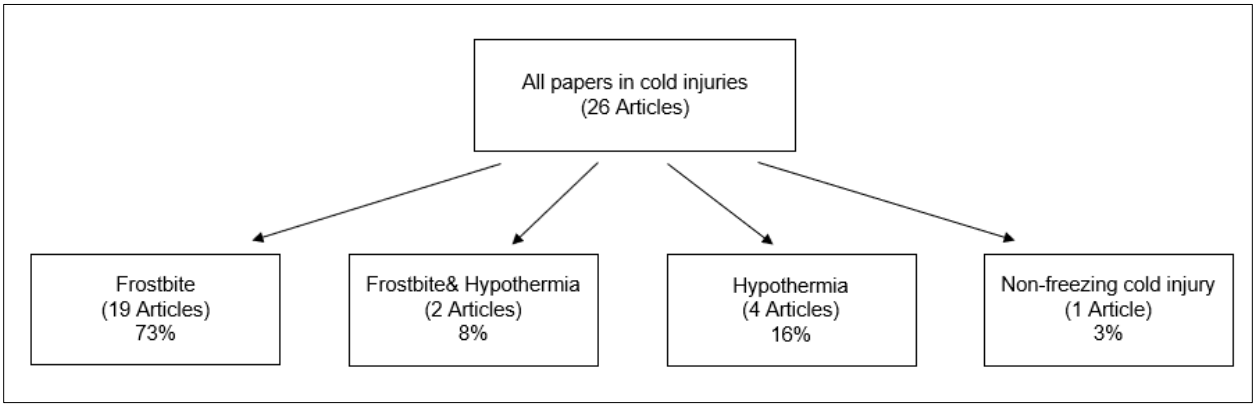

Figure 3: The categories of cold injury papers

Results for the Web of Science search appear in Figure 4. Forty-five papers were found, and 25 of them related to the cold injuries.

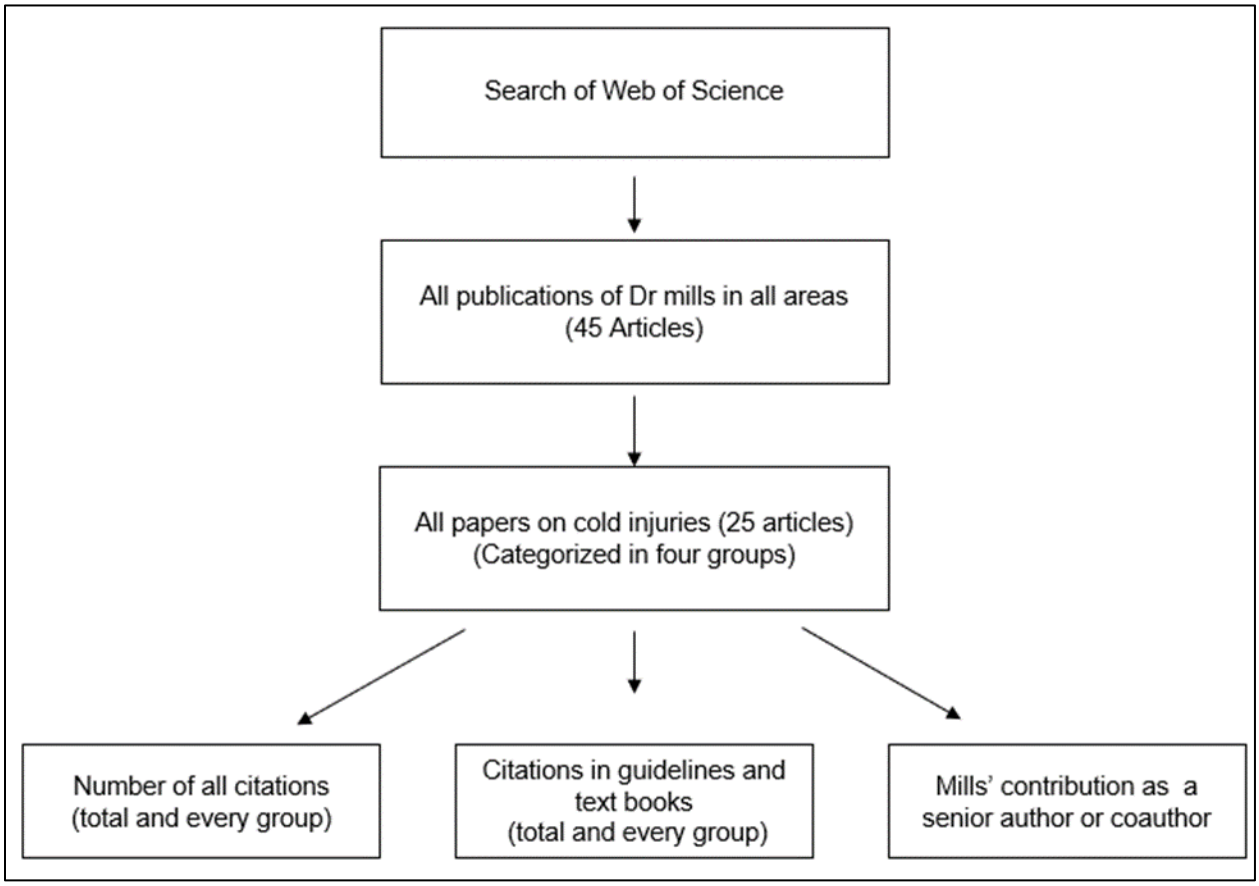

Figure 4: Search of Web of Science.

Finally, four clinicians and researchers provided feedback on how Dr. Mills affected their careers. They included Drs. Ken Zafren, Dan Danzl, Murray Hamlet, and Gordon Giesbrecht.

REVIEW OF PAPERS (FROSTBITE)

Pathophysiology

In 1993, Dr. Mills divided the pathology of frostbite into two stages: Stage 1, the cooling, supercooling, and freezing; and Stage 2, thawing (rewarming) and post-thaw (vascular stage) [42]. The first stage begins with vasoconstriction after exposure to cold and ends in freezing. When freezing occurs, ice crystals form in the extracellular space and osmotic pressure increases in the extracellular space. This increase results in the absorption of intracellular water and produces intracellular and extracellular dehydration. As cooling and freezing continues, cell membrane damage occurs and permeability of cell wall increases. Endothelial cell injury occurs and endothelium separates from the internal elastic lamina of the arterial wall. In the second stage (thawing and post-thaw), three important events include vasodilatation, edema, and stasis. Changes due to reperfusion injury, arachidonic acid cascade, thromboxane, and prostaglandins result in vascular clotting and tissue ischemia [42].

Classification

The four-degree classification was applied in frostbite similar to burn terminology used in the past. A variety of signs were listed to determine the "degree" of frostbite and plan the treatment. Even the experienced clinician had difficulty classifying frostbite injury. In 1960, Dr. Mills and his colleagues simplified the classification to two degrees instead of a four-degree classification. They divided freezing injury into superficial and deep to make the classification easier and more practical for field use. Superficial frostbite is limited to the skin and it corresponds to the first- and second-degree frostbite in the traditional classification. Deep frostbite involves tissues under the skin, including nerve, blood vessel, muscle, tendon, and bone. Deep frostbite corresponds to the traditional third- and fourth-degree frostbite [3].

Treatment

Dr. Mills established a protocol in 1955 for treating frostbite patients. He published the results of four years of research to Tech Rep Arct Aeromed Lab US in 1959 [43]. Nevertheless, this paper was not published until April 1960 when Dr. Mills had already published the protocol of treatment based on 5 years of experience in the first of three papers in March 1960 in a new journal (Alaska Medicine) [2].

In 1973, he divided treatment into two parts, before thawing, and after thawing [44]. Before thawing, treatment included rapid thawing in warm water or warm wet packs (a cotton cloth is dipped in warm water then and it is wrung out and wrapped around the frozen part) if nothing was available. After thawing, further care was applied when the injury was deep and hospitalization was necessary. These subsequent treatments included some modalities such as daily whirlpool baths and physiotherapy to avoid infection and improve tissue preservation and joint function. Rapid rewarming as an initial treatment was ordered when the affected part was frozen however when the affected part was already thawed, further rewarming would not be applied [44].

Mills recommended frozen parts should be protected from trauma. He described three conditions in which thawing should be postponed: 1) if severe freezing occurred and walking on frozen feet was not avoidable, it would be better to leave the limb frozen because travel on the thawed part that is swollen, painful, hyperemic and blistered is difficult or impossible; 2) he recommended avoiding thawing an extremity if there was the risk of refreezing because the outcome of refreezing is very poor and usually results in amputation. Indeed, he suggested that if severe frostbite occurred, the limb may best be left in its frozen state until being rescued or getting a shelter; and 3) If there was a chance to thaw by rapid thawing in a short time it would

be reasonable to delay thawing until getting rapid thawing instead of using other slower methods for thawing [4].

Rapid rewarming. (Initial treatment)

In the first papers which offered a protocol for the treatment of frostbite, Dr. Mills explained three important factors for tissue injury in frostbite. The first and most obvious was the actual disruption of cellular and tissue structure due to ice crystal formation. The second was dehydration and the third was impaired circulation in the recovery phase of frostbite. He explained how rapid rewarming would affect two of three factors (structural damage and circulation impairment) [2].

Dr. Mills noted that previous laboratory studies had demonstrated that the tissue injury was greater when the cooling time was longer and particularly when the rate of rewarming was slow [2]. However, the most impressive study which affected his protocol was Meryman's research at The United States Naval Medical Research Institute. Meryman had demonstrated that the size of ice crystals formed in tissues was inversely proportional to the rate of freezing, therefore prolonging the state that tissue was partially frozen and ice crystals were in equilibrium with the tissue fluid resulted in slow accretion to ice crystals with a growth in their size and more tissue damage [41]. Dr. Mills also referred to the meatpacking industry that recognized that rapid freezing and maintenance in very low temperatures is necessary for the proper preservation of food. Therefore, it could be concluded that the maintenance of tissue at its freezing point, usually -2º to -5ºC, may be more detrimental than the maintenance of this tissue at a much colder temperature.

Another factor that was affected by slow warming was circulatory impairment. Based on finding from laboratory experiments in animals, circulatory impairment was the most important factor in tissue injury after freezing. These studies demonstrated that circulation impairment was most evident when tissue temperature was +5º to +15ºC so it was reasonable to avoid prolonged maintenance of tissue at this temperature. Thus, based on these explanations it would be rational to recommend if thawing started it should be very fast to normal body temperature to decrease the structural and circulation disruption [2].

Dr. Mills advised rapid thawing by immersing in a warm water bath at temperatures from 42º to 48ºC (110º to 118ºF) that contained hexachlorophene-containing detergent [2]. He investigated the outcomes of treatment of four methods of thawing: rapid rewarming by immersing in warm water, delayed thawing (thawing with ice and snow), gradual thawing (thawing at room temperature), and thawing by excessive dry heat. In the first series of papers, the results of treatment of 51 patients who were treated by Dr. Mills were published. 37 cases thawed their frozen extremity at room temperature, and 6 subjects thawed the extremity in ice water (delayed thawing) (Table 5). One subject used excessive heat for thawing. Of 51 subjects just 7 received rapid rewarming. Outcomes showed that the subject who used excessive heat had early mummification and vast amputation. 66% of the delay thawing group had an anatomical amputation and 50% had major amputations. Of the rapid warming group only 14% had anatomical amputation without any major amputation. Major amputation was defined as phalangeal amputation at any level in four or more, complete phalangeal loss at metacarpal or metatarsal-phalangeal junction, or amputation of the extremities.

Table 5. Outcomes for frostbite patients treated with 4 different rewarming methods. Studies are from 1961 (n=51) and 1973 (n=200).

	Year of study	Number of cases	No residual effects	Some residual effect[1]	Amputation
Rapid rewarming	1961	7	0%	86% (6)	14% (1)
	1973	48	10% (5)	86% (41)	4% (2)
Slow thawing	1961	37	9% (3)	51% (19)	40% (15)
	1973	132	9% (12)	61% (81)	30% (39)
Delayed thawing	1961	6	17% (1)	17% (1)	66% (4)
	1973	16	6% (1)	25% (4)	69% (11)
Thawing by excessive heat	1961	1	0%	0%	100% (1)
	1973	4	0%	0%	100% (4)

[1]Dysesthesia, intrinsic muscle atrophy, skin loss requiring replacement skin cover, or limitation of joint motion greater than 25%.

The results demonstrated that rapid rewarming had the best outcomes in deep frostbite. The dry heat was very destructive in both superficial and deep injuries because of the danger of increasing tissue temperatures above the limit of viability and superimposing a burn injury on tissue that was previously injured by severe cold. Except for dry heat, superficial injuries could be treated with any type of rewarming and there was not a significant difference in results. Gradual rewarming at room temperature and thawing with ice had poor outcomes in deep injuries and mostly resulted in tissue loss [3].

1973, Dr. Mills published the results of treatment of 200 frostbite patients whom he had personal treated. In this study 48 frostbite cases received rapid rewarming and 132 slow rewarming,16 patients had delayed thawing and 4 patients used excessive heat [45] (Table 5).

The percentage of amputation for the rapid rewarming group was just 4%, delayed group 69%, and for excessive heat 100%. These results again demonstrated that rapid rewarming was the best method for thawing.

Frostbite treatment prognosis differed based on the method of thawing. In order of prognosis from best to worst: 1) rapid rewarming by immersion in water; 2) gradual thawing usually at room temperature; 3) delayed thawing or thawing by utalizing ice and snow; and 4) thawing by excessive heat (50ºC or higher). Thawing by rapid rewarming in warm water was the best choice for thawing because of the greatest tissue preservation [44].

Dr. Mills treated 1026 frostbite patients by 1993 with his protocol and applied rapid rewarming for all frozen extremities. He published a thorough explanation for the treatment of frostbit and affirmed the effectiveness of rapid rewarming in greater tissue preservation [46].

Rapid rewarming was more painful than gradual rewarming in its initial stage; it caused more hyperemia and larger blebs. The pedal pulses often were "pounding" after warming, and the blebs usually extended to include even the terminal phalanges. Because of the extreme reaction, particularly the formation of edema and blebs, he stated this method may not be a "trail therapy" for use in the field [4] [47].

Rapid rewarming continued to be the fundamental part of the treatment of frostbite with some alteration in water temperature. In the first paper, the temperature for the water was 42 to 48ºC [2]. Then, Dr. Mills reported that the temperature of less than 42ºC was unsatisfactory and greater than 49ºC was too hot. Then he reduced the maximum recommended temperature and recommended a range between 42º and 46ºC [47]. Dr. Mills continued to decrease the recommended in the following years, Dr. Mills stated 46ºC and any level above that was too

warm and temperatures over 49ºC (120ºF) were very harmful, so his new recommended water temperature was between 42º and 44ºC (107º to 112ºF) [48]. In a report of 200 patients, the temperature was reduced to 38º to 42ºC (100º to 108ºF) [45]. In 1983, based on observation of 800 patients treated for frostbite, a final water temperature ranging from 38º to 41ºC (100º to 106ºF) was recommended [49]. This temperature remained the recommended temperature in his following papers [46] [50].

Whirlpool bath therapy

In the first paper, the whirlpool bath was recommended for physiotherapy and applying ultrasound in a water environment. The whirlpool bath which contains Hexachlorophene detergent was applied twice daily for 20 minutes and during each bath the patient was encouraged to exercise the extremities because this was easier during the baths [2]. The results were impressive (Table 6). The use of the whirlpool with a detergent, decreased the prevalence of severe infection in comparison with the patients who did not receive a whirlpool bath. In addition, gentle movement of water detached the dead tissues that were already ready for separation. In other words, it performed a physiological atraumatic debridement as well as stimulating massage of tissues. It caused rapid diminishing of edema due to increasing local circulation and pain was relieved after serial whirlpool sessions [3] [4].

Table 6. Outcomes of the effects of whirlpool bath on infection from the 1961 study (n=51)

	Number of cases	No clinical infection	Superficial infection	Deep infection
Any methods with whirlpool bath	29	48% (14)	52% (15)	0% (0)
Any methods without whirlpool bath	22	45% (10)	14% (3)	41% (9)

In the first paper, the whirlpool temperature for bathes were 37º to 38ºC (98º to 100ºF), then the temperature decreased to 32º to 35ºC (90º to 95ºF) [2] [44]. The temperature did not change in the subsequent years [46].

Physiotherapy

Active exercises of digits were recommended after thawing as soon as possible. In this protocol, physiotherapy was instituted by encouraging digit exercise utilizing bedside physiotherapy and during whirlpool baths to improve the range of joint motion after thawing but passive manipulation was postponed to after the acute phase [2].

Ultrasound therapy

Dr. Mills and his colleagues believed once initial rewarming was accomplished, secondary changes such as fibrosis of intrinsic muscles, sludging of blood, thrombosis of vessels, and irreparable changes in peripheral nerves were the most important problems that should be prevented [2].

They used a potent tool that had not previously been employed for frostbite, ultra-high frequency sound. The major advantage of ultrasound over conventional diathermy was the deep penetration of tissues. In their opinion, ultrasound usage permitted penetration to all deep structures of the extremities, including bone. Assuming that the condition of deep structures would be the determining factor in the outcome of the freezing injury, it seemed logical to include ultrasound as a modality in the treatment of frostbite to direct the treatment to the injured, but still viable, deep structures, especially vessels and nerves, as well as bone and intrinsic musculature including tendons [2]. Ultrasound was applied in dosages varying between 1-1.5 W/cm^2 in a water medium, with the sound head as close as possible without contacting the

extremity. The application of this high-frequency sound was prescribed for five minutes once or twice daily within the bath [2].

The results of using ultrasound were that ultrasound was not as useful as had been expected, and they found ultrasound both helpful and a hindrance. In cases of superficial injury, there was subjective evidence of benefit. Some patients reported "improved" sensation and ease of interphalangeal joint motion. However, there were some signs and symptoms in deep injuries after ultrasound treatment like pain, and necrosis. Thus, it was concluded that the use of ultrasound in deep injuries was harmful. Therefore, they reported that ultrasound was beneficial in superficial injury but it was not useful and could even be harmful in deep injury. Ultrasound was never applied in the following years [3] [4].

Antibiotics

Dr. Mills reported in the first papers that patients were routinely placed on broad-spectrum antibiotics (as occurs with open fractures) for the first four years of their study. Subsequently however, antibiotics were ordered only after definite indication and based on culture and sensitivity studies because the outcomes showed that their use was not necessary for the majority of patients utilizing whirlpool bath therapy [43] [4].

It was presumed this happened because the germicidal agent (hexachlorophene) in the bath reduced the numbers of bacteria and disrupted their metabolism. Therefore, it decreased the incidence and severity of pyogenic skin infection. Using an open method during treatment (without dressing) and avoiding early-stage debridement could prevent infection too. After these findings, Mills used antibiotics only after a definite diagnosis, based on culture and sensitivity testing [3] [4].

Debridement and amputation

The effects of early debridement on ultimate outcomes and tissue preservation were studied in the first series of papers [4]. Incision of edematous and friable tissue increased the risk of infection by bacteria that already presented on the skin. The results of the first series of papers (Tables 7 and 8) demonstrated poor outcomes after debridement. The ultimate outcomes were poor in those patients who were infected and debrided, or who were debrided and developed infection following debridement. Debridement or amputation in the early stages (first to the third week) should be avoided. Whirlpool baths provided debridement adequately and physiologically. The gentle motion of the water removed eschar when it was released from the epithelializing bed and it was ready for physiological separation. The only condition that debridement (escharotomy) could be beneficial in, was when dry eschar retracted and caused necrosis, muscle atrophy, or joint motion restrictions [3] [4].

Table 7. Debridement and infection from 1961 study (n=51).

	Number of cases	No residual effects	Some residual effects[1]	Amputation
Not debrided and not infected	21	14% (3)	76% (16)	10% (2)
Not debrided and infected	5	0%	80% (4)	20% (1)
Debrided and not infected	4	0%	50% (2)	50% (2)
Debrided and infected prior to debridement	7	14% (1)	43% (3)	43% (3)
Debrided, without prior infection and infected after debridement	14	0%	7% (1)	93% (13)

[1]Dysesthesia, intrinsic muscle atrophy, skin loss requiring replacement skin cover, or limitation of joint motion greater than 25%.

Table 8. Effects of debridement on ultimate results from 1961 study (n=51).

	Number of cases	No residual effects	Some residual effect[1]	Amputation
Without debridement	26	12% (3)	76% (20)	12% (3)
With debridement	25	4% (1)	24% (6)	72% (18)

Dr. Mills (1983) recommended that debridement or amputation be delayed for 30 to 90 days [49]. He explained debridement or amputation should be delayed until the line of demarcation has formed. This usually happens often within 15 to 45 days [46].

Fasciotomy

In 1973, Dr. Mills added a new area in the treatment of frostbite. He described that if the extremity had been in the frozen state for a long time even rapid rewarming and other supportive care would not be able to restore the circulation and a compartment syndrome may occur. Therefore, fasciotomy might be necessary to prevent circulation disruption [44].

Sympathectomy

Dr. Mills performed unilateral lumbar surgical sympathectomies, in patients with estimated equal bilateral lower extremity freezing injury. He usually performed the procedure within twenty-four to forty-eight hours of thawing. On the side of the sympathectomy not only were edema and pain less than on the other side but they also decreased more rapidly on the side of the procedure. Bleb formation receded more rapidly in the sympathectomized side and demarcation occurred earlier than on the other side. However, the ultimate tissue loss is similar on both sides and there was no further preservation of tissues [48].

In the following years, Dr. Mills performed unilateral post-thaw lumbar and cervical sympathectomies within 12 hours to three weeks in patients with a bilateral similar extremity injury. Outcomes were the same as in the previous study [45]. Mills (1983) performed this procedure within the first 24 to 48 hours. The alteration of sympathectomy timing did not affect the results. Thus, the first 24 to 48 hours remained as the standard timing for sympathectomy [49].

Dr. Mills (1983) offered pharmacological sympathectomy by using phenoxybenzamine hydrochloride (Dibenzylene). This drug is an effective α-adrenergic blocking agent and had already been used for vasospasm. In subsequent years, Dr. Mills suggested that surgical and pharmacological sympathectomy may have a good effect following fasciotomy [49].

Skin graft

Dr. Mills published the results of his studies on skin grafts for the first time in 1973 [45]. He applied skin grafts to improve healing between the third and twenty-first days after thawing while it could be used for reconstruction at any time. Dr. Mills reported that split-thickness skin grafts took well during the early stages of healing if the method of thawing was rapid rewarming. However, skin grafts were irregularly successful after spontaneous or delayed thawing by snow or ice. The procedure of grafting could be considered in many cases to prevent exposure and consequent necrosis of tendons and underlying fascia and joints [45]. The time of grafting later changed to the third to the fourteenth day after thawing and with the conclusion that the best results of grafting occur after rapid warming [49].

Drugs

Dr. Mills explained three important and basic aspects for the treatment of frostbite: rapid rewarming; vascular therapy, and miscellaneous (hospitalization and subsequent treatments). Vascular therapy including anticoagulants, vasodilators, and sympathectomy (blocking the sympathetic nerve supply to the injured area) was applied in a few cases in the early years of study in 1950s but use of drugs was discontinued because there were no beneficial effects [43].

However, use of drugs was always one of Mill's interests and in subsequent years, he assumed that there were three types of post-thaw injuries: 1) vasoconstriction after thawing; 2) arterio-venous-capillary thrombosis after injury; and 3) cell destruction (Mills 1983). With these injury types in mind, he offered anticoagulants (heparin), hypotensive adrenergic blocking agents (Guanethidine Reserpine), vasodilators (Priscoline), and sympatholytic drugs (Dibenzyline). He found Dibenzyline effective in vasospasm as an alpha-adrenergic blocking agent for treatment of vasoconstriction. Dr. Mills proposed that the use of thrombolytic enzymes (Streptokinase, Urokinase) for deep thrombosis should be evaluated. He explained "The risk of hemorrhage and lysis of fresh fibrin may limit the use of these drugs with associated trauma, especially in head trauma where the cerebral vascular bleed may be of concern". He suggested that the administration of these drugs needed special techniques. There was no drug offered for cell destruction [49].

Dr. Mills later expanded the list of the drugs used in frostbite injury care including: plasma volume expanders (low molecular weight dextran); hypotensive agents (guanethidine, reserpine); vasodilating agents (tolazoline hydrochloride); hemorheological agents (oxpentifylline); sympatholytic agents (phenoxybenzamine hydrochloride); calcium blocking agents (nifedipine); anticoagulating agents (heparin); an industrial solvent (dimethyl sulfoxide

DMSO); thrombolytic enzymes (streptokinase, tissue plasminogen activator TPA); anti-inflammatory agents such as nonsteroidal drugs, and acetylsalicylic acid, Ibuprofen [46].

Dr. Mills observed that there was no clear treatment for preventing injury secondary to the formation of oxygen free radicals, damaging neutrophils, or reperfusion injury. He believed this area should be considered as an important cause of injury and investigated [46].

Biofeedback

Applied psychophysiology represents a science that uses bio-behavioral methods to achieve the self-regulation of physiology through learning techniques. Thermal biofeedback training is one of the bio-behavioral methods that was used for self-regulation of peripheral vasoconstriction for the prevention and treatment of cold injuries [51]. Based on thermal biofeedback training, the skin temperature could be an indicator of vasodilatation. The average skin temperature on dorsal digital surface at rest for healthy females was 88ºF and for healthy males was 92ºF. Patients with medical history of frostbite, thermal disorders, or distressed individuals had lower extremity skin temperatures ranging between 60º to 70ºF. It was demonstrated most of these patients could increase digital skin temperature by 20º F after ten to fifteen half-hour training sessions of biofeedback (total of 5 to 7.5 hours) [51].

Dr. Mills used biofeedback training for labile vasomotor changes and intermittent vasoconstriction cases starting in 1976. These techniques were applied in warming some post-thawed frozen digits and continued to be part of the Providence Hospital frostbite treatment protocol [52]. In 1984 thermal biofeedback training on frostbite patients in addition to the basic treatment of frostbite resulted in increases in the foot temperatures in patients due to improvement of blood circulation to the injured area [53]. In this study, patients received

instructions on four different types of relaxation exercises including progressive breathing and guided Imagery. Patients were required to practice one or more of these methods twice a day before biofeedback training. Patients practiced thermal biofeedback twice a day for 20 to 25-minute periods.

In 1982, a study started in the Denali Project to investigate the effectiveness of biofeedback in providing peripheral vasodilatation on demand in extremities to prevent cold injury. People who had learned to improve thermal regulation in the low temperature had less skin temperature decrease and more stability in comparison to those without training, or with only indoor training during cold exposure [52]. Dr. Mills reported that biofeedback training can be an option for the prevention of stress and providing vasodilatation on demand for people who are in danger of cold injury, especially in very stressful circumstances (e.g., military operations). However, transferring the heat from the core to the extremities can reduce the core temperature, so using biofeedback for an extended time can cause hypothermia [52].

Silver nitrate

After Moyer's publication about using Silver Nitrate 0.5% for burn injuries, Dr Mills studied the effect of this treatment for six years for freezing injury. It was applied to one side of bilateral injuries, of similar magnitude, in hands or feet. Dr. Mills reported that silver nitrate 0.5% decreased pain and infection but that epithelialization was similar to that produced by the surgical soaps [44].

Silver sulfadiazine

Dr. Mills (1983) reported that he had been using 1% silver sulfadiazine on open wounds caused by freezing injury, when severe drying and bleeding occurred due to superficial infection.

Silver sulfadiazine prevented eschar separation by inhibiting proteolytic enzyme bacterial growth [49].

Categorization of frostbite

Dr. Mills (1983) recognized seven types of Alaskan frostbite injury: 1) true frostbite, superficial or deep; 2) a mixed injury, immersion injury (wet-cold injuries) followed by freezing: this injury is disastrous and painful and there is considerable tissue loss; 3) freezing, thawing, and refreezing injury: this injury is generally disastrous and tissue loss is noticeable with early mummification of distal tissues (in a week or less); 4) high-altitude environment injury: extremity freezing accompanied by hypoxia and often dehydration of tissues. Prognosis is poor, especially if associated with compartment pressure syndrome; 5) freezing superimposed on fracture, dislocation, or severe extremity injury: if the fracture, dislocation is left unreduced, outcomes will be poor; 6) freezing superimposed on the extremity with compartment pressure from any cause: very poor results will be obtained if compartment pressures syndrome is not treated ; and 7) hypothermia superimposed with freezing [49].

Diagnostic tools

<u>Radioisotope Scan.</u>

In 1960, Dr. Mills and his colleagues conducted pilot studies on approximately twenty normal individuals to determine the blood flow in cold-injured extremities. They demonstrated the efficiency of radioisotope scans in blood flow determination. They recommended utilizing this tool in assessing the degree of injury, prognosis, and effects of therapy in the cold injury for the first time [4]. From 1960 to 1973, the use of technetium 99 became a routine to determine cellular perfusion and tissue viability and to aid in diagnosis and prognosis of frostbite injury in

Alaska [54]. Radioisotope examination (technetium 99m) remained as a diagnostic tool for the status of injury and presence, or absence of perfusion in the affected tissue after freezing injury.

X-Ray.

Dr. Mills (1993) reported that significant changes in bone and cartilage were observed after freezing injury. This change was not apparent at the early stage, even when the x-rays were repeated after 3 to 5 months did not show any changes. For several years, just one x-ray was taken (flat plate) from feet and hands at the onset of freezing. These x-rays were all normal. However, radiographic changes appeared in the x-rays from six to l8 months. Changes ranged from large areas of avascular necrosis of bone to small punctate, lytic changes in affected digits. Mills recommended that every frostbite patient should have a series of x-rays from early to late stages to identify any lesions that were due to freezing. The x-ray file would help to rule out other diagnoses in the future if those lesions were discovered independently [46].

Prognosis

Dr. Mills identified factors that predict the prognosis of freezing injury in 1993. Factors favoring a good prognosis included: short duration of freezing, superficial depth of injury, freezing without any other insult (fracture, hypothermia, immersion injury, or other trauma), the existence of large and distal clear blebs after thawing, and early return of perfusion after thawing (especially if detected by technetium 99 radioisotope studies) [46].

Factors predicting a worse prognosis included: long duration of freezing, superimposing frostbite on other traumas (fracture or dislocation, or soft tissue trauma), and association with an existing medical condition (vascular deficiency, hypovolemia, or hypoxia).

Factors predicting the worst prognosis included: delayed thawing (ice, snow, friction massage), thawing by excessive heat (higher than 49ºC), the existence of proximal, dark, hemorrhagic blebs after thawing, early necrosis with early mummification within 4 to 5 days, perfusion deficiency (detected by technetium 99 studies on early and follow-up views), and freeze-thaw-refreeze injury [46].

Future research

Dr. Mills considered freezing and hypothermia to be reperfusion injuries. He assumed that oxygen free radicals were involve and that activated neutrophils were incriminated in endothelial injury during reperfusion. He recommended that oxygen free radicals, activated neutrophil, and other inflammatory and immune responses be investigated in the future as responsible elements in cold injury damage [42].

The endothelial cell structure is very important because a single layer of endothelium lines the entire circulatory system. The normal endothelium wall forms a smooth and tight surface on the luminal side. The intact endothelium is a semipermeable membrane for material to interchange between blood and tissues while preventing the larger elements from leaving the vessels. Any injury of the endothelium impacts flow patterns, alters permeability, and causes the release of substances that enhances clot formation [50].

RIEVIEW OF PAPERS (HYPOTHERMIA)

Pathology

Hypothermia is defined as a reduction in core temperature to less than 35ºC. Cases of survival from hypothermia as low as 13.7ºC have been reported [55]. The first response to the

cold is piloerection and vasoconstriction, then following more cooling, muscle tension and shivering. Shivering is triggered by skin cooling even at a core temperature of 37 [56]. Shivering results in increased metabolism because of shivering work, ventilation, and raised cardiac output. Shivering increases as core temperature decreases to about 32°C but when cooling continues and core temperature reduces to lower temperature shivering decreases and stops at a core temperature of about 30°C.

Clinical symptoms of hypothermia relate predominantly to cerebral and cardiorespiratory effects. At approximately 35ºC incoordination and stumbling occur and when core temperature drops below about 34ºC, dysarthria occurs, and it seems the victim talks with a mouthful of mush. When cooling continues at 32.2º to 31.1ºC the person slides to the semi-comatose phase when the heart cools below 30°C, cardiac output decreases significantly and bradycardia usually occurs [57].

Initially, during cold stress, metabolism increases by inducing shivering. Heart rate, blood pressure, and consequently oxygen consumption also rises. When the cold becomes overwhelming for the body the thermal stress and hypothermia initiate. The function of the control system of the acid-base level decreases and acidosis begins to appear. Metabolic acidosis causes oxygen consumption to decrease, for example at 30ºC, oxygen consumption is decreased by 50% [50].

Mills (1980) created the term “metabolic icebox”. He explained that when the core temperature decreases to, and below, 29ºC, the function of all vital systems is decreased. Cerebral and cardiorespiratory functions are particularly depressed, so their aerobic metabolism needs are also reduced, therefore the body can survive the oxygen consumption reduction and this stage may continue for hours (if on land, and much less in water immersion). Dr. Mills

explained that the metabolic icebox is a mid-lethal state whereas, more cooling may result in death due to cardiorespiratory failure, uncontrolled warming can end in death due to electrolyte imbalance [58].

Death in hypothermia commonly happens because of ventricular fibrillation. It is an uncoordinated, lethal contraction of the ventricles. Dr. Mills stated that this arrhythmia is not a direct effect of cold. Rather it is due to changes in the electrolytes and pH of the blood [58].

Treatment

Field care.

The first responder who encounters a hypothermic victim should remove the victim from the wind and place them in a tent, snow cave, snow shelter, slip trench, or windbreak. All wet clothing should be removed, and the responder should attempt to clothe the victim in dry clothing [57]. Dr. Mills suggested that if the victim is alert and can swallow, warm sugary fluids should be given [57]. Dr. Mills recommended that the rescuer should prevent heat loss, but it is not reasonable to add heat rapidly. Adding heat rapidly in the field without physiological control may result in cardiac arrhythmias due to imbalance electrolysis which is not treatable in the field. Unfortunately, "rapid heat" was not well defined, and this advice led to the mistaken understanding that any warming in the field could be dangerous. Dr. Mills later clarified that "rapid heat" included warm water immersion and that most heat source available in the field (e.g., chemical heat packs, warm water bottles or bags, etc.) were not considered "rapid heat" and were indicated for the treatment of cold patients.

Dr. Mills stated that in the victim with no signs of life, the general rules for shelter and dry clothing still apply. Some closed-chest manipulation and mouth-to-mouth resuscitation

should be tried, and it should be considered to transport to a medical facility if there is no danger to the rescuer. The patient is dead only when warm and dead because the physiologic effects of hypothermia (e.g., bradycardia and coma) are deceptive, and an alive person may appear dead. Therefore, we can be sure about the victim's death only after rewarming. However, transport to medical facility and prolonged CPR may not be possible in an isolated environment [57].

Medical facilities.

In 1980, Dr. Mills published a historical review of fifty cases of hypothermia in Alaska and described a management approach to the treatment of hypothermia. It was obvious the most important part of the treatment of hypothermia was control of metabolic and cardiac and chemical issues which appear during and after rewarming. The duration of this control could be up to three to eight hours in slow warming methods or short thirty minutes to two hours in rapid rewarming methods [58].

Treatment included: 1) rewarming; 2) physiological control including airway, monitoring cardiac performance, blood gases, and electrolytes. Therefore, under total physiological control, the method of rewarming and the depth of hypothermia (even to the level of 21.1ºC) were not important. Several methods for warming could be applied including: 1) external passive warming: warm shelter, dry clothing, blanket, and insulted mats; 2) external active warming: warm blankets, warming cradles, radiant heat, rapid rewarming in a tub or whirlpool bath; 3) internal (intracorporeal) warming: warm enemas, gastric lavage, inhalation of warm moist oxygen (38 -43ºC) or warm intravenous solution (38-41ºC); and 4) internal (extracorporeal) warming: peritoneal dialysis hemodialysis [59].

REVIEW OF PAPERS (NON-FREEZING COLD INJURY)

Pathophysiology

Immersion injury, otherwise referred to as non-freezing cold injury (NFCI) was seen in 105 of 1282 cold injured patients from 1961 to 1993 (Table 9) [46]. It can happen due to salt or freshwater exposure, usually at low temperatures near, but not at, freezing levels. Four stages have been described for NFCI [60]. These four stages include: 1) during cold exposure: the affected extremities are "numb" and swollen. The skin color first is "red" in appearance, Limbs but soon become pale or white due to severe vasoconstriction. Sensation and proprioception are lost. Sometimes they have trouble walking; 2) the pre-hyperemic (post initial warming) stage: feet are numb, edema may happen. The skin color changes to mottled and pale blue, indicating the return of circulation at a very low level. This stage can last from a few hours to many days; 3) the hyperemic stage: numbness is eventually replaced by tingling, aching, pain, and intermittent throbbing. The limb is bright red and swollen. Blister formation and gangrene may occur in injured areas that have suffered pressure injury or infection. This stage may last six to ten weeks; 4) the post-hyperemic stage: inflammation reduces, vascular tone recovers, and skin temperature decreases. The extremities are cold-sensitive with Raynaud's phenomenon or digital blanching. This stage may last for weeks and even months, and in some cases, for years.

Treatment

Immersion injury, or NFCI, was described by many scientists as a disease of nerves and muscle [61]. However, in the Alaska series, group microscopic and examination on tissue samples from fasciotomy or partial amputation found many changes in blood vessels. Therefore, acute and long-term treatment must include restoration of circulation. Treatment includes: 1) treatment of compartment syndrome if indicated, by applying fasciotomy to release the tissue

from pressure; 2) use of medications that improve vessel dilatation and loss of sympathetic effect to help decrease edema and reduce edema pain; 3) drugs that relieve severe pain as in epidural blockade; and 4) the prevention of infection by applying the whirlpool bath and gentle care of the extremities [61].

From 1961 to 1993, Dr. Mills had treated 1282 cold injury patients: 1026 had frostbite, 151 were hypothermic, and 105 had immersion injuries (NFCIs). Fifty-four patients in a hypothermic state had frozen extremities, while another group of 15 hypothermia victims had associated immersion (wet-cold) injury. Twenty-five immersion injury victims had superimposed freezing injury. Six hypothermic patients had pre- existing immersion injury with superimposed freezing injury Table 9 shows the categories of cold injuries and their numbers.

Table 9: Cold injuries from 1282 cases between 1961 and 1993. Cases involve either a single or combination of two types of injury; [46].

	Frost bite	Hypot hermia	Immersion injury (NFCI)
Frostbite	1026	54	25
Hypotherm ia	-	151	15
Immersion injury	-	-	105

SEARCH OF WEB OF SCIENCE

Report of total papers

The search was done on the Web of Science for Dr. Mills' publications. Forty-five papers were found. These papers are about several subjects including frostbite, hypothermia, immersion (NFCI), high altitude, and orthopedics.

These papers have been cited 787 times with an average of 17.5 per paper. Dr. Mills had an H- index of 11 (Table 10). Figure 5 shows citations and publications together based on the year.

Table 10: Web of Science publication information.

Total papers	Citation times	Average per item	H-Index
45	787	17.49	11

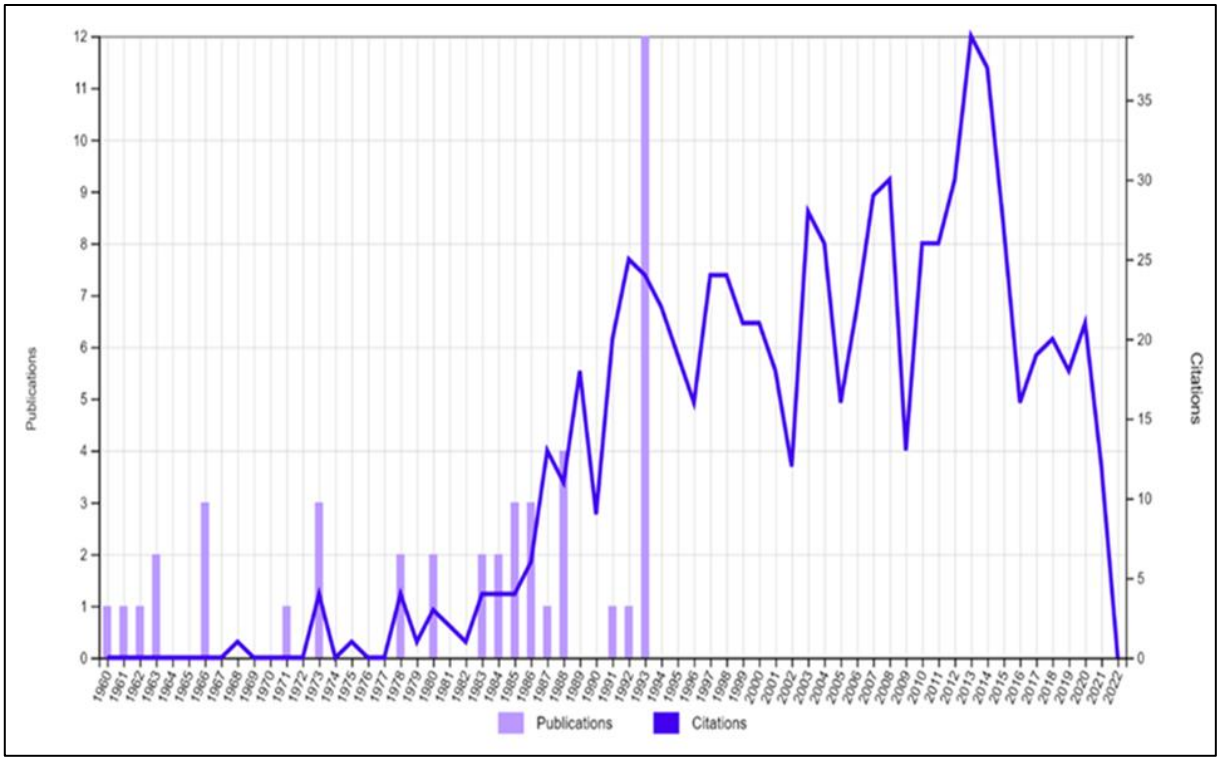

Figure 5: Publications and citations chart based on year for total papers

Report of cold injury papers

Twenty-five of forty-five papers are on frostbite, hypothermia, and immersion injury (NFCI). These papers are divided based on their subjects into four groups: frostbite, hypothermia, frostbite and hypothermia, and immersion injury (the same categories were used in the review of papers). Some points are notable in this list.

The original version of three papers that were published in 1960 and 1961 are not in this list and the reprint of these papers, which were published in 1993, are included (e.g., n=12). There are 4 papers that are included twice on the Web of Science because their original publication and reprint version both are included.

The 25 papers consist of 18 on frostbite, 2 on frostbite and hypothermia, 4 on hypothermia, and one on immersion injury (NFCI). These 25 papers were cited 126 times (96

for frostbite, 11 for frostbite and hypothermia, 12 for hypothermia, and 7 for immersion injury). These papers were cited in cold-related guidelines 11 times (9 for frostbite and 2 for frostbite and hypothermia) and 4 times in books (3 for frostbite and one for hypothermia). Dr. Mills is the senior or sole author in 21 papers and coauthor for 4 (Table 11).

The results for the number of publications and their citation based on the year were obtained for 25 papers. Figure 6 shows citations and publications together for 25 papers.

Table 11: Results for Search of Web of Science

	Number of papers	Citations number	Citations in guidelines	Citations in books	The senior author	The only author	The coauthor
Total	25	126	11	5	21	15	4
Frostbite	18	96	9	4	14	9	4
Frostbite and hypothermia	2	11	2	0	4	4	0
Hypothermia	4	12	0	1	4	4	0
Immersion injury (NFCI)	1	7	0	0	1	0	0

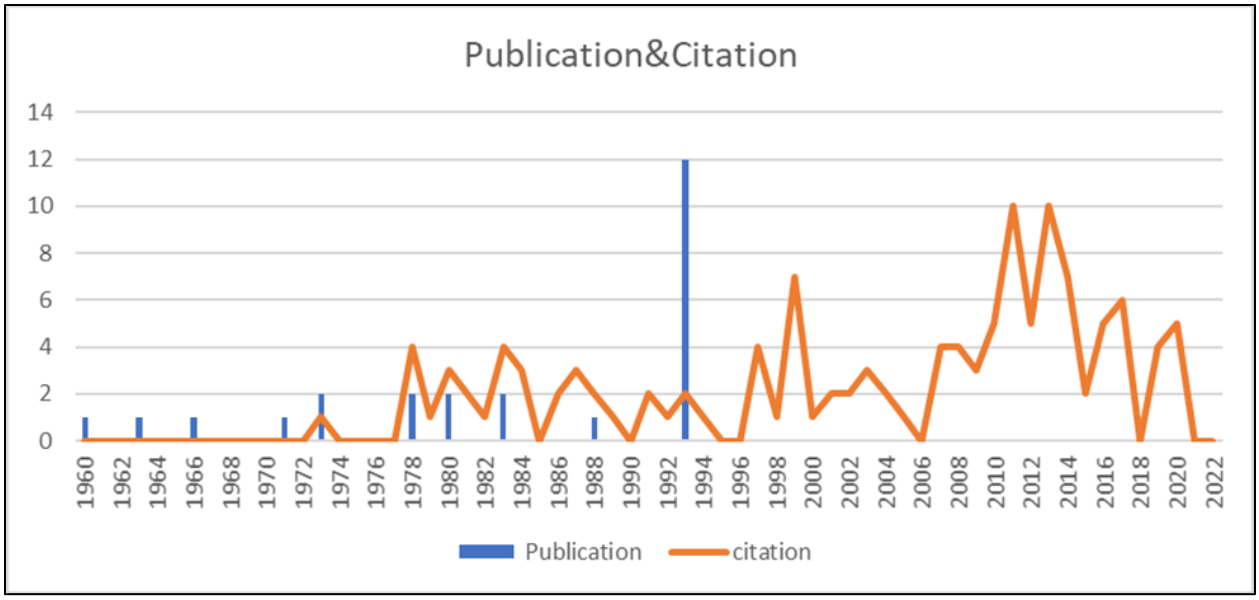

Figure 6: Publications and citations chart based on year for cold injury papers (n=25)

INFLUENCE ON RESEARCHERS AND CLINICIANS

Some coauthors of publications with Dr. Mills were contacted and were asked to comment about Dr Mills' influence on the care of frostbite in general and on their personal practice.

Dr. Ken Zafren

Clinical Professor, Department of Emergency Medicine, Stanford University

Staff Emergency Physician, Alaska Native Medical Center, Anchorage

Emergency Programs Medical Director, State of Alaska 2001-2017

"Bill Mills became interested in the treatment of frostbite in 1955 after seeing patients in Alaska who had undergone amputations after sustaining frostbite. He observed wide variations in treatment from packing the frostbitten part in ice to the application of local heat. He also

noted that the approaches to amputation varied from "considered watchful neglect" to early amputation above the site of demarcation.

Inspired by the work of Harold Meryman on tissue freezing and thawing at the United States Naval Medical Research Institute, Bill set out to study the best methods of treating frostbite. He concluded that rapid thawing in warm water caused the least tissue damage, and that delayed amputation gave better results than early amputation. He published his work in Alaska Medicine in a 3-part article in 1960 and 1961.

Although similar research was ongoing in Scandinavia and in the Soviet Union, Bill's influence extended at least to western Europe. Rapid thawing in water and delayed amputation spread rapidly across North America and western Europe, supplanting all other methods. In 1992, Jacques Foray from Chamonix, France, published a huge case series of 1261 cases, stating that rapid rewarming is a keystone of therapy.

When I began practicing emergency medicine in Anchorage, Alaska in 1994, I started to see patients with frostbite. Bill was officially retired. Frostbite patients requiring admission at the 2 private hospitals where I worked all went to Jim O'Malley, a general surgeon. Jim had trained informally with Bill and still consulted Bill on complex cases. I was determined to learn as much about frostbite as I could, so for a year, I followed Jim O'Malley on his rounds, seeing almost every admitted frostbite patient. Bill was often present on these rounds or in the operating room. As an orthopedic surgeon, Bill would assist Jim with amputations.

Almost everything I learned about the care of frostbite came from Bill Mills, directly or indirectly. I had the good fortune to write the Wilderness Medical Society teaching presentation on Frostbite with Jim O'Malley and Bill Mills as my coauthors. Bill also helped Gordon

Giesbrecht and me to write the frostbite section of the Alaska Cold Injuries Guidelines in 2003. The Alaska guidelines are still used worldwide."

Dr. Daniel Danzl

Professor and Emeritus Chair, University of Louisville School of Medicine

"Bill Mills MD's innumerable contributions to Wilderness Medicine include the challenging of Napoleon's Surgeon-in-chief Baron de Larrey's caveats about rapid thawing and rewarming. Dr. Mills' 1961 publication in Alaska Medicine continues to impact the treatment of frostbite and hypothermia.

Personally, his effect on my career was profound. He graciously agreed to be one of my co-investigators which resulted in being awarded an Office of Naval Resources grant in 1983-85. The data published from the Multicenter Hypothermia Survey in 1987 continues to be cited. In the subsequent decades, we collaborated frequently in didactic and research venues. To my amazement, at the end of his career, he sent me an entire set of his research slides."

Dr. Murray Hamlet

The retired director of the Cold Research Division for the US Army Research Institute of Environmental Medicine (Natick MA)

Bill Mills single-handedly established the present standard care for frostbite. The protocol calls for rapid rewarming with 110º F water, twice daily whirlpool baths, and avoiding early surgery leaving blisters intact. No one has added any significant improvement to this management. He added some pharmaceuticals later. He knew what worked and what did not. The whole focus was to salvage as much tissue as possible. Deviation from this protocol brought quick repute from Bill. Although frostbite was his major interest, Bill contributed significant

pieces to hypothermia management. Many of his patients had both hypothermia and frostbite, and he had to treat both concomitantly.

His primary goal was tissue salvage. His treatment was to wait for demarcation and assured no viable tissue was removed by an overzealous surgeon. His methods and success have not been improved upon. Frostbite is a kind temperature injury. His work proved that freeze and refreeze was a devastating injury. History has shown that this sequence has debilitating results. As an example of the destructive results of this procedure, cryosurgery uses this technique to remove skin tumors today. Mills presented at cold injury conferences because of the spread of discussion and new approaches needed to be defended with scientific data or results. Any modeling of frostbite is extremely difficult. The conclusions are hard to validate with clinical results.

He did discussions on urokinase, streptokinase, heparin, aspirin, DMSO, steroids, hypobaric O2 and many other techniques were engaged with minimum value in clinical management. He clearly understood what worked what did not. Physical destruction of the capillary bed was the key and the only thing that would improve tissue salvage would be the recovery of those capillary beds, rebuilding them or regrowing them.

Mills volunteered to be a field surgeon in the Vietnam War. A little-known fact was that he has hundreds of war surgery photographs that he took during his employment. He was also considered a bit of a deity in the native population of Alaska. He treated many patients without a fee. He considered lawyers to be scabs on society and held them in great disdain. When the Veterans' Administration did not consider that cold injury justified compensation, he quickly joined the group of physicians who worked to help get hundreds of old soldiers to get compensation for their war-inflicted cold injury.

Early on in my career, Dr. Mills didn't think I had much to add to the field because I was a veterinarian, but as the years went on and we discussed issues and he realized I could do laboratory studies that he couldn't do such as the effect of urokinase and streptokinase and other drugs. We developed a meaningful relationship where we talked about what might work and what might not work.

Bill had a significant impact on my research with animal modelling. He encouraged me to study more and more substances to let him know if they worked or not. In most cases, his clinical judgement was proven by our studies. His main conclusion was that the most important factor in tissue loss or salvage was the physical loss of capillary beds, and other factors were not as important. He knew that intuitively and we proved it with animal models of the vascular bed.

He knew that treatments like hyperbaric oxygen and application of DMSO (both treatments directly delivered oxygen to tissues but did not improve oxygenation after treatment was complete) would not work in the long term if the vascular bed was destroyed. Whenever I would tell him that I was working on a new treatment, he would always start by asking, "does it improve capillary blood flow?" and if it didn't, the discussion was essentially over because he wasn't going to listen to it, it didn't matter.

Nobody has done anything better with frostbite management than I've ever seen. His emphasis to keep surgeons away from patients early on has saved so many amputations. Surgeons felt that anything that was black had to be cut off. Mills believed that if there was anything under that black surface that could be saved, it should be. I was very honored that he gave me a copy of his frostbite slides before he died (I have since given them to Helge Brandstrom in Sweden). That collection was amazing, nobody else has anything like that.

Dr. Gordon Giesbrecht

Professor, Faculty of Kinesiology and Recreation Management and Departments of Emergency Medicine and Anesthesia, University of Manitoba.

Bill Mills was a giant in clinical research and treatment of frostbite. He had gained a reputation in the 1950s and 60s and by the time I entered academia in the late 1980s he was a legend. I had read some of his papers and heard great stories about him from colleagues like Murray Hamlet. I organized a "Clinical consensus meeting on cold injuries" in Winnipeg in 1999 and invited many experts from North America and Europe. I was extremely honored and excited when Dr. Mills accepted my invitation. There were about a dozen giants in the field of hypothermia and frostbite at the meeting, but he was the Dean of the group. Whenever he spoke, everyone else listened. I was honored when I was asked to participate in the updating of the Alaska Guidelines for treatment of hypothermia, frostbite, and other cold injuries in 2003. I am very proud that I am listed as a coauthor with him on this publication.

It was easy to listen to Bill because, not only was he scientifically qualified, but his dry sense of humor made for great entertainment. Several years ago, I nominated him for an honorary degree from the University of Manitoba. Thankfully, the University approved my nomination and Dr. Mills accepted the invitation to receive it. Unfortunately, he became ill just before he was scheduled to receive the doctorate at one of our convocations. It is university policy that an honorary degree cannot be awarded in absentia, but only posthumously. I am glad our president Dr. Emőke Szathmáry organized a special convocation at the University of Alaska (Anchorage) where we could make the award in front of his family and friends. It was a great event. When Bill got up to give his reception speech, he noted that he was aware of our policy that if he couldn't come to Winnipeg, we didn't award honorary doctorates in absentia but would

only do so posthumously. He thanked us for coming to Anchorage because he didn't like the idea of receiving it posthumously.

Certainly, Bill's giant contributions and presence at any meeting will be missed.

SUMMARY

Dr. William J Mills Jr changed the treatment of frostbite from delayed thawing that was offered by Baron Larrey to rapid rewarming after 140 years. This study investigated the contribution of Dr. Mills to the treatment of frostbite by reviewing his papers, investigating in Web of Science, and finding researchers who were influenced by Dr. Mills.

All Dr. Mills' papers were obtained from the Medline database and the University of Alaska medical library. Then papers were divided based on inclusion criteria (frostbite, hypothermia, and cold injury) and exclusion criteria (orthopedics, high altitude, or not related to cold injury). Articles that met inclusion criteria were categorized into four groups: frostbite, frostbite & hypothermia, hypothermia, and immersion injury (NFCI). All cold injury papers were reviewed and summarized in an annotated bibliography.

A search on Web of Science was done and H index and citation number and publication number were obtained for all his publications. Then, the cold injury papers were investigated separately to find out the number of citations, citations in textbooks, and citations in guidelines. Dr. Mills' contribution to cold injury papers as a senior author or co-author was reported as well.

Some co-authors who had publications with Dr. Mills were contacted to have comments on Dr. Mills' influence on the treatment of frostbite generally and on their careers.

Furthermore, this study provided a historical review of the treatment of frostbite and laboratory research that investigated scientific understanding of rapid rewarming in the treatment of freezing injury. Besides providing details of the initial protocol of treatment of frostbite created by Mills in 1960, the modalities which were removed or added to this protocol during three decades were recorded.

Dr. Mills innovated a treatment in the 1950s based on results of laboratory findings and his clinical knowledge. Throughout decades he improved that treatment protocol. This protocol has not been changed significantly and is applied with a few alterations after nearly sixty years. Dr. Mills for more than forty years (by 2001) treated or consulted more than 1500 cold injury cases including more than 1000 frostbite cases. His publications have been cited in guidelines and textbooks.

The most important modalities and recommendations for the treatment of frostbite which are recommended in the treatment of frostbite guideline 2019 and created by Dr. Mills are listed in Table 12.

Table 12: Dr. Mills' modalities and recommendations in the new Guideline (2019)

1. Rapid rewarming
2. Antibiotics (based on culture and signs)
3. Anticoagulants
4. Thrombolytics
5. Vasodilators
6. Fasciotomy (based on signs of compartment syndrome)
7. Amputation (delay in amputation for one to three months)
8. Debridement (avoiding of debridement)
9. Tetanus prophylaxis
10. Whirlpool bath (Hydrotherapy)
11. Physiotherapy

REFRENCES

1. Paton, B.C., *"From Larrey to Mills": the road to rapid rewarming-a commentary.* Wild. Environ. Med., 1998. **9**: p. 223-225.
2. Mills, W.J., Jr. and R. Whaley, *Frostbite: experience with rapid rewarming and ultrasonic therapy: Part I.* . Alaska Med, 1960. **35**(1): p. 6-9.
3. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part II.* . Alaska Med, 1960. **35**(1): p. 10-8.
4. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part III.* . Alaska Med, 1961. **35**(1): p. 19-27.
5. Lorentzen, A.K., C. Davis, and L. Penninga, *Interventions for frostbite injuries.* Cochrane Database Syst Rev, 2020. **12**: p. Cd012980.
6. Endorf, F.W. and R.M. Nygaard, *High Cost and Resource Utilization of Frostbite Readmissions in the United States.* J Burn Care Res, 2021. **42**(5): p. 857-864.
7. Valnicek, S.B., L.R. Chasmar, and C.J. B, *Frostbite in the praries: A 12 year review.* Plastic and Reconstructive Surgery, 1993. **92**: p. 633-641.
8. Mills, W.J., *Clinical aspects of freezing cold injury*, in *Medical Aspects of Harsh Environments*. 2001. p. 429-466.
9. Weatherley-White, R.C., B. Sjostrom, and B.C. Paton, *Experimental studies in cold injury.II. the pathogenesis of frostbite* J Surg Res, 1964. **4**: p. 17-22.
10. Meryman, H., *Tissue freezing and local cold injury.* Physiol. Rev., 1957. **37**: p. 233-51.
11. Zacarian, S.A., D. Stone, and M. Clater, *Effects of cryogenic temperatures on microcirculation in the golden hamster cheek pouch.* Cryobiology, 1970. **7**(1): p. 27-39.

12. Handford, C., O. Thomas, and C.H.E. Imray, *Frostbite.* Emerg Med Clin North Am, 2017. **35**(2): p. 281-299.

13. Hallam, M.J., et al., *Managing frostbite.* Bmj, 2010. **341**: p. c5864.

14. Hutchison, R.L., *Frostbite of the hand.* J Hand Surg Am, 2014. **39**(9): p. 1863-8.

15. Larrey, D.J., *Surgical Memoirs of the Campaigns of Russia, Germany and France*. 1832, Philadelphia: Carey & Lea, .

16. Imray, C., A. Grieve, and S. Dhillon, *Cold damage to the extremities: frostbite and non-freezing cold injuries.* Postgrad Med J, 2009. **85**(1007): p. 481-8.

17. Rodway, G.W., S.E. McIntosh, and W. Askew, *Bradford washburn's 1962 NEJM article "Frostbite: what is it-how to prevent it-emergency treatment"-historical background and commentary.* Wilderness & environmental medicine, 2010: p. 1-5.

18. Ariev, T.J., *Monograph on Frostbite*. 1955, Canada: Defense Research Board.

19. Zafren, K., *Dr. William J. Mills, Jr. July 7, 1918 – December 4, 2011*, in *Response*. 2012, EMS: Alaska. p. 1.

20. Hild, C.M., Jr., *A leading authority on cold injuries in Alaska.* Int J Circumpolar Health, 2004. **63**(3): p. 212-3.

21. Woo, E.K., et al., *Proposed treatment protocol for frostbite: a retrospective analysis of 17 cases based on a 3-year single-institution experience.* Arch Plast Surg, 2013. **40**(5): p. 510-6.

22. Reamy, B.V., *Frostbite: review and current concepts.* J Am Board Fam Pract, 1998. **11**(1): p. 34-40.

23. Némethy, M., et al., *Mt Everest Base Camp Medical Clinic "Everest ER": epidemiology of medical events during the first 10 years of operation.* Wilderness Environ Med, 2015. **26**(1): p. 4-10.

24. McIntosh, S.E., et al., *Mountaineering medical events and trauma on Denali, 1992-2011*. High Alt Med Biol, 2012. **13**(4): p. 275-80.

25. Copass, M., et al., *State of Alaska cold injuries guidelines*. 2003, Department of Health and Social Services Division of Public Health Section of Community Health and EMS: Alaska. p. 1-60.

26. Mohr, W.J., K. Jenabzadeh, and D.H. Ahrenholz, *Cold injury.* Hand Clin, 2009. **25**(4): p. 481-96.

27. McIntosh, S.E., et al., *Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite: 2019 Update.* Wilderness Environ Med, 2019. **30**(4s): p. S19-s32.

28. Lewis, T., *Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues: I. Reactions to Cold, and Injury of Normal Skin.* Br Med J, 1941. **2**(4222): p. 795-7.

29. Lewis, T., *Observation upon reactions of the vessel of the human skin to cold.* Heart, 1930. **15**: p. 177-208.

30. Brown, R.T. and J.G. Baust, *Time course of peripheral heterothermy in a homeotherm.* Am J Physiol, 1980. **239**(1): p. R126-9.

31. Marzella, L., et al., *Morphologic characterization of acute injury to vascular endothelium of skin after frostbite.* Plast Reconstr Surg, 1989. **83**(1): p. 67-76.

32. Lewis, R.B., *Pathogenesis of muscle necrosis due to experimental local cold injury.* Am J Med Sci, 1951. **222**(3): p. 300-7.

33. Quintanilla, R., F.H. Krusen, and H.E. Essex, *Studies on frost-bite with special reference to treatment and the effect on minute blood vessels.* Am J Physiol, 1947. **149**(1): p. 149-61.

34. Zook, N., et al., *Microcirculatory studies of frostbite injury.* Ann Plast Surg, 1998. **40**(3): p. 246-53; discussion 254-5.

35. Robson, M.C. and J.P. Heggers, *Evaluation of hand frostbite blister fluid as a clue to pathogenesis.* J Hand Surg Am, 1981. **6**(1): p. 43-7.

36. Mazur, P., *Cryobiology: the freezing of biological systems.* Science, 1970. **168**(3934): p. 939-49.

37. McCauley, R.L., J.P. Heggers, and M.C. Robson, *Frostbite. Methods to minimize tissue loss.* Postgrad Med, 1990. **88**(8): p. 67-8, 73-7.

38. Cauchy, E., et al., *Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme.* Wilderness Environ Med, 2001. **12**(4): p. 248-55.

39. Cauchy, E., et al., *The role of bone scanning in severe frostbite of the extremities: a retrospective study of 88 cases.* Eur J Nucl Med, 2000. **27**(5): p. 497-502.

40. Paton, B.C., *Cold, casualties, and conquests: the effects of cold on warfare*, in *Medical aspects of harsh environment*. 2001. p. 313-349.

41. Meryman, H.T., *Mechanics of freezing in living cells and tissues.* Science, 1956. **124**(3221): p. 515-21.

42. Mills, W.J., Jr., J. O'Malley, and B. Kappes, *Cold and freezing: A historical chronology of laboratory investigation and clinical experience.* Alaska Med., 1993. **35**: p. 89-116.

43. Mills, W.J., Jr., J.D. Douglas, and A.W. Gottmann, *Clinical experiences in treatment and rehabilitation of frostbite in Alaska.* Tech Rep Arct Aeromed Lab US, 1960. **59-24**: p. 1-9.

44. Mills, W.J., Jr., *Summary of treatment of the cold injured patient.* Alaska Med, 1973. **15**(2): p. 56-9.

45. Mills, W.J., Jr., *Frostbite. A discussion of the problem and a review of an Alaskan experience.* Alaska Med, 1973. **15**(2): p. 27-47.

46. Mills, W.J., Jr., *Comments on this issue of Alaska Medicine--from then (1960) until now (1993).* Alaska Med, 1993. **35**(1): p. 70-87.

47. Mills, W.J., Jr., *A study of frostbite treatment* J R Nav Med Serv, 1963. **49**: p. 237-43.

48. Mills, W.J., Jr., *Frostbite. A method of management including rapid thawing.* Northwest Med, 1966. **65**(2): p. 119-25.

49. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Frostbite.* Alaska Med, 1983. **25**(2): p. 33-8.

50. Mills, W.J. and R.S. Pozos, *Low temperature effects on humans.* Encyclopedia of Human Biology, 1997. **5**(2): p. 383-401.

51. Kappes, B., W. Mills, and J. O'Malley, *Psychological and psychophysiological factors in prevention and treatment of cold injuries.* Alaska Med, 1993. **35**(1): p. 131-40.

52. Mills, W.J. and D. Rau, *University of Alaska, Anchorage-section of high latitude study, and the Mt. Mckinley Project (1981-82-83).* Alaska Med, 1983. **25**(2): p. 21-8.

53. Kappes, B.M. and W.J. Mills. *Thermal biofeedback training with frostbite patients*. in *Circumpolar Health 84*. 1984.

54. Mills, W.J.J., *Comment and Recapitulation.* Alaska Med., 1993. **35**: p. 69-88.

55. Gilbert, M., et al., *Resuscitation from Accidental Hypothermia of 13.7 °C with Circulatory Arrest.* The Lancet, 2000. **355**(9201): p. 375-376.

56. Zafren, K., et al., *Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 Update.* Wilderness Environ Med, 2014. **25**(4): p. 425-45.

57. Mills, W.J., *Field care of the hypothermic patient.* Int. J. Sports Med., 1992. **13**(Suppl. 1): p. S199-S202.

58. Mills, W.J.J., *Accidental hypothermia: management approach.* Alaska Med, 1980. **35**(1): p. 54-6.

59. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Hypothermia.* Alaska Med, 1983. **25**(2): p. 29-32.

60. Ungley CC, Channell GD, and R. RL., *The immersion foot syndrome.* Br J Surg., 1945. **33**(129): p. 17-31.

61. Mills, W.J., Jr. and W.J. Mills, 3rd, *Peripheral non-freezing cold injury: immersion injury.* Alaska Med, 1993. **35**(1): p. 117-28.

APPENDIX

ANNOTATED BIBLIOGRAPHY

Table of Contents

FROSTBITE (19 articles)

1. Mills, W.J., Jr., J.D. Douglas, and A.W. Gottmann, *Clinical experiences in treatment and rehabilitation of frostbite in Alaska.* Tech Rep Arct Aeromed Lab US, 1960. **59-24**: p. 1-9.
2. Mills, W.J., Jr. and R. Whaley, *Frostbite: experience with rapid rewarming and ultrasonic therapy: Part I.* . Alaska Med, 1960. **35**(1): p. 6-9.
3. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part II.* . Alaska Med, 1960. **35**(1): p. 10-8.
4. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part III.* . Alaska Med, 1961. **35**(1): p. 19-27.
5. Mills, W.J., Jr., *A study of frostbite treatment* J R Nav Med Serv, 1963. **49**: p. 237-43.
6. Mills, W.J., Jr., *Frostbite. A method of management including rapid thawing.* Northwest Med, 1966. **65**(2): p. 119-25.
7. Sessions, D.G., et al., *Frostbite of the ear.* Laryngoscope, 1971. **81**(8): p. 1223-32.
8. Mills, W.J., Jr., *Frostbite. A discussion of the problem and a review of an Alaskan experience.* Alaska Med, 1973. **15**(2): p. 27-47.
9. Wilson, R., et al., *Death on Denali.* West J Med, 1978. **128**(6): p. 471-6.
10. Franz, D. R., et al., *Evaluation of fasciotomy and vasodilator for treatment of frostbite in the dog.* Cryobiology, 1978.**15**(6): p. 659-669.
11. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Frostbite.* Alaska Med, 1983. **25**(2): p. 33-8.

12. Mills, W.J. and D. Rau, *University of Alaska, Anchorage-section of high latitude study, and the Mt. Mckinley Project (1981-82-83).* Alaska Med, 1983. **25**(2): p. 21-8.
13. Kappes, B. M. and W. J. Mills, *Thermal biofeedback training with frostbite patients.* Circumpolar Health, 1984. **84**(1): p. 83-84
14. Foutch, R.G. and W.J. Mills, Jr., *Treatment and prevention of cold injuries by ancient peoples indigenous to arctic and subarctic regions.* Arctic Med. Res, 1988. **47**(Suppl.1): p. 286-289.
15. Kappes, B.M. and W.J. Mills, *A sample of personality profiles of frostbite patients in Alaska 1980-86.* Arctic Med. Res, 1988. **47**(Suppl. 1): p. 243-245.
16. Mills, W. J., Jr, *Comments on this issue of Alaska Medicine--from then (1960) until now (1993).* Alaska Med, 1993. **35**(1): p. 70-87.
17. Mills, W. J., Jr, *Frostbite and hypothermia--current concepts. 1973.* Alaska Med, 1993. **35**(1): p. 28.
18. Mills, W.J., Jr., J. O'Malley, and B. Kappes, *Cold and freezing: A historical chronology of laboratory investigation and clinical experience.* Alaska Med., 1993. **35**: p. 89-116.
19. Kappes, B., W. Mills, and J. O'Malley, *Psychological and psychophysiological factors in prevention and treatment of cold injuries.* Alaska Med, 1993. **35**(1): p. 131-40.

FROSTBITE&HYPOTHERMIA (2 papers)

20. Mills, W.J., Jr., *Summary of treatment of the cold injured patient.* Alaska Med, 1973. **15**(2): p. 56-9.
21. Mills, W.J. and R.S. Pozos, *Low temperature effects on humans.* Encyclopedia of Human Biology, 1997. **5**(2): p. 383-401.

HYPOTHERMIA (4 papers)

22. Mills, W.J.J., *Accidental hypothermia: management approach.* Alaska Med, 1980. **35**(1): p. 54-6.

23. Samuelson, T., et al., *Hypothermia and cold water near drowning: Treatment guidelines.* Alaska Med, 1982. **24**(6): p. 106-11.

24. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Hypothermia.* Alaska Med, 1983. **25**(2): p. 29-32.

25. Mills, W.J., *Field care of the hypothermic patient.* Int. J. Sports Med., 1992. **13**(Suppl. 1): p. S199-S202.

IMMERSION INJURY (NON-FREEZING COLD INJURY) (one paper)

26. Mills, W. J. and W. I. Mills, *Peripheral non-freezing cold injury: immersion injury.* Alaska Medicine. **35**(1): p. 117-28.

Frostbite

1. Mills, W.J., Jr., J.D. Douglas, and A.W. Gottmann, *Clinical experiences in treatment and rehabilitation of frostbite in Alaska.* Tech Rep Arct Aeromed Lab US, 1960. **59-24**: p. 1-9.

Dr. Mills explained rewarming followed by long physiotherapy which was applied in 25 frostbite subjects during 4 years. This paper was the first article that offered rapid warming. It was issued by the Arctic aeromedical laboratory in October 1959 for official use. These results were published in a more detailed and complete explanation in three papers in 1960 and 1961. Dr. Mills' protocol included: 1) Rapid rewarming in warm water 43º to 49ºC (110º to 120ºF) for 20 minutes or until thawing happens after thawing the affected area cleaned by antiseptic soap; 2) Antibiotics used for two weeks (Penicillin); 3) patient was required to exercise joints actively after thawing as soon as extremities can be touched passive physiotherapy started by physiotherapist; 4) Whirlpool bath twice every day 43ºC (110º F); 5) ultrasound was applied in whirlpool bath 1 to 1.5 w/q. Mills recommends diathermy (ultrasound) for the preservation of deep structures that improves deep; 6) vasodilators and anticoagulants and sympathectomy were employed in a few cases but it did not continue. Mills explained early debridement and amputation can have destructive effects. Results of patients who were treated by this method despite very deep involvement did not have amputation greater than one or two phalanxes but records from Alaska hospital from other patients who treated by other methods all too often had amputation above or under the knee.

2. Mills, W.J., Jr. and R. Whaley, *Frostbite: experience with rapid rewarming and ultrasonic therapy: Part I.* . Alaska Med, 1960. **35**(1): p. 6-9.

This article was the first part of three articles that offered a treatment protocol including rapid warming and ultrasonic therapy for frostbite. In this article, the authors explained the background and methods. Their treatment consisted of several important elements 1) rapid warming by immersing in a warm water bath at temperatures 42º to 48ºC (110º to 118ºF). Whirlpool bath was usually used to provide more rapid heat; 2) precise care was taken to prevent blebs rupture and trauma. After cleaning the affected part with a germicidal solution, sterile sheets were used to cover the part. The dressing was not used but for prevention of maceration small pledges of sterile cotton were placed between fingers and toes; 3) whirlpool baths were given for 20 minutes once or twice daily one to two weeks baths contained Hexachlorophene detergent to remove the surface bacteria. These baths were combined with physiotherapy 4) physiotherapy was instituted with encouraging digits exercise utilizing bedside physiotherapy to improve range of joints after thawing 5) ultrasonic treatment was used in dosage of 1-1.5 watts per square centimeters in a water medium the sound head as close as possible without contacting the extremity the application of this high-frequency sound was prescribed for five minutes once or twice daily within the bath 6) antibiotics were utilized in the same doses and for the same rationale as are ordered in open fractures.

3. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part II.* . Alaska Med, 1960. **35**(1): p. 10-8.

This paper is the second part of three papers that offered a treatment protocol including rapid warming, ultrasonic therapy for frostbite. In this article, the authors described subjects and results. Fifty-one cases of frostbite were studied for five years. forty-one were treated directly by senior author Dr. Mills as either the attending or consulting physician. The remaining subjects were drawn from the files of the Alaska Native Service Hospital or from Providence Hospital Anchorage. The majority of patients were male, in the fifteen to forty-five years age range. Seven patients received the full program of treatment (rapid rewarming, whirlpool bath, physiotherapy, ultrasound). Seven patients received all treatments except rapid rewarming. Six subjects received whirlpool bath and physiotherapy. Thirty patients were treated with other methods than this protocol. Classification of initial injury was divided into two degrees superficial and deep. Outcomes were evaluated based on the ultimate injury which was classified into four stages: A) no recorded or demonstrated residual; B) dysesthesia: a. intrinsic muscle atrophy b. skin loss requiring skin cover c. limitation of joint motion greater than 25%; C) phalangeal amputation any level three or less; D) phalangeal amputation four or more, complete amputation in metacarpal or metatarsal phalangeal junction, major loss of extremity" authors investigated the effect of different methods of thawing on the ultimate injury. Moreover, they recorded the impact of whirlpool bath and physiotherapy, ultrasound therapy, debridement on the final outcomes.

4. Mills, W.J., Jr., R. Whaley, and W. Fish, *Frostbite: experience with rapid rewarming and ultrasonic therapy. Part III.* . Alaska Med, 1961. **35**(1): p. 19-27.

This is the third part of a series of papers that offered a treatment protocol including rapid warming, ultrasonic therapy for frostbite. In this paper, the authors provided results and discussion, and the conclusion part. Outcomes of different methods of thawing showed that dry heat is very destructive in both superficial and deep injuries except for this method, superficial injuries could be treated with any type of rewarming and there was not a significant difference in results. However, in deep injuries, the best results were from rapid warming in a warm bath at the temperature of 43º to 48ºC (110º to 118ºF). Gradual rewarming at room temperature and thawing with ice had poor outcomes and mostly resulted in tissue loss. Regardless of the method of thawing or rewarming, utilizing a whirlpool bath containing detergent had several useful effects it cleaned the surface bacteria, provides physiological debridement and relief of pain, and made digit exercises easier. Physiotherapy improved the motion of the digits and the return of a more normal sensation. Ultrasound as a form of deep tissue massage was beneficial in superficial injury nevertheless it was not useful even it might be harmful in deep injury. Using antibiotics was not necessary for patients who were applying whirlpool baths. Any type of debridement and amputation was prohibited at the period of 6 to 21 days. Whirlpool was adequately and physiologically performed debridement except for one indication for debridement could exist when dry eschar retracts and tightens and cause necrosis, muscle atrophy, or joint motion restrictions. Amputation if must be done it should be in 60 to 90 days after injury. Antibiotics were not essential in patients utilizing whirlpool baths and in recent years authors used antibiotics just only for definite infections based on culture and sensitivity exams.

Authors recommended if severe frostbite happened in a trail and further travel was necessary it would be better for the limb might be left in a frozen state because after thawing travel would be difficult there would also be a risk for refreezing.

5. Mills, W.J., Jr., *A study of frostbite treatment* J R Nav Med Serv, 1963. **49**: p. 237-43.

This article gives a summary of the treatment method which was created in three papers in 1960 then provides some alteration in some points based on the author's experience throughout the years after first publication. Fifty-one cases of frostbite between 15 to 45 years of age, were studied for five years. Forty-one were treated directly by senior author Dr mills as either the attending or consulting physician the remaining subjects were drawn from the files of the Alaska Native Service Hospital or from Providence Hospital Anchorage the predominant factor for exposure to cold was accidents such as vehicular accidents or breakdown, runaway dog teams, falling through the ice wall. Method of treatment includes rapid thawing in warm water is the best method of thawing for deep injuries. the temperature of the water should be between 43º to 46ºC (110º to 115º F) for 20 to 40 minutes (in the original paper temperature is 43º to 48ºC (110º to 118º F)) the temperature less than 110º is unsatisfactory and the upper than 120ºF is hot. whirlpool baths combined with physiotherapy were given for 20 minutes once or twice daily in water temperature 37º to 43ºC (98º to 110ºF) for one or two weeks. Physiotherapy was instituted with encouraging digits exercise actively after thawing but passive manipulation was postponed to after acute phase. Ultrasonic treatment was used for five minutes once or twice daily within the bath. outcomes showed in deep injuries the best results are from rapid warming but in superficial injuries, all methods are acceptable except dry heat. whirlpool baths containing detergent are beneficial to prevent infection, provide physiological debridement and relief of pain. physiotherapy improves the motion of the digits and the return of a more normal sensation. Ultrasound is useful in superficial injury however it can be harmful in deep injuries.

6. Mills, W.J., Jr., *Frostbite. A method of management including rapid thawing.* Northwest Med, 1966. **65**(2): p. 119-25.

The author updated the frostbite treatment and explained some alterations in the method. He discussed the effects of new adjuncts that are applied in the past few years. The treatment method included rapid rewarming and a daily whirlpool bath combined with physiotherapy. Observation on more frostbite subjects demonstrates temperature range of thawing may vary from 37º to 44ºC (98º to 112ºF), however, 115ºF and any level above that was too warm and temperatures over 120ºF were very harmful. Dr. Mills recommended 42º to 44ºC (107º to 112ºF) as the appropriate temperature. Whirlpool bath 37º to 38ºC (98º to 100ºF) includes hexachlorophene or povidone-iodine (Betadine) was given twice a day throughout the therapy. Physiotherapy included the exercise of digit joints separately and in accompany by whirlpool baths throughout the treatment. Antibiotics were utilized only if evidence of clinical infection was indicated and based on culture and sensitivity tests.

There was not any significant profit in the usage of vasodilators, anticoagulants, sympathetic block in the acute or sub-acute phase. These medications were helpful in the late phase, six months to two years or more in patients who were not thawed by rapid warming.

Unilateral lumbar sympathectomies were applied, in patients with equal bilateral lower extremity freezing injury. The procedure has been done usually within twenty-four to forty-eight hours of thawing. The results demonstrated that on the side of the sympathectomy edema and pain were less than other side and they reduced rapidly. However, the ultimate tissue loss is similar on both sides.

7. Sessions, D.G., et al., *Frostbite of the ear.* Laryngoscope, 1971. **81**(8): p. 1223-32.

The results of the treatment of 32 patients during 15 years 1955 to 1970 was provided in this paper. The method of treatment was rapid rewarming with warm wet sterile cotton pledges in 38º to 42ºC (100º to 108º F). Silver nitrate 0.5 % was used for superficial injuries dressing was not used. Sedatives were used for pain and antibiotics were used just in presence of infection. Anticoagulants, vasodilators, and enzymes were not effective in treating the frozen ear. Surgical debridement was avoided if it was needed.

Results showed that in twenty-four patients with superficial frostbite there was not any permanent tissue loss. Nine patients were rapidly thawed and fifteen patients were thawed spontaneously at room temperature. Eight patients with deep frostbite who were not treated by rapid warming had either permanent auricular cartilage abnormality or tissue loss. Results showed that there is no significant difference between rapid warming and slow thawing in superficial injuries to the ear however authors recommend rapid warming as the best method for deep injuries.

Poor prognosis signs include cyanotic cold ear, delayed appearance of small dark blebs, and apparent mummification. Good prognosis signs include warmth and presence of sensation after thawing and early appearance of large clear blebs.

8. Mills, W.J., Jr., *Frostbite. A discussion of the problem and a review of an Alaskan experience.* Alaska Med, 1973. **15**(2): p. 27-47.

Two hundred cases of frostbite were investigated based on the method of treatment and outcomes in this study. One hundred thirty (130) cases were treated by Mills' method seventy (70) patients were treated by other methods. Forty-six (46) subjects received a full program consisting of rapid rewarming in the whirlpool in 38º to 42ºC (100º to 108ºF), physiotherapy, daily whirlpool therapy (90º to 98ºF), and open care. Eighty-four (84) patients received the whole program except rapid warming. Results showed that the rapid rewarming program had better outcomes in comparison with other methods based on ultimate injury and rapid rewarming had significant effects on results.

The post-thaw lumbar and cervical sympathectomy were performed between 12 hours to three weeks in patients with a bilateral similar injury to extremities on one side only. In sympathectomy side edema and infection rapidly improved, and severity and duration of pain decreased in comparison with another side however more preservation of tissue often happened in the extremity not subjected to ganglionectomy. Silver Nitrate 0.5% was lavaged in one side of bilateral injuries in hands or feet which were in the same depth. Silver nitrate decreased pain and infection nevertheless the epithelialization was similar. Skin grafts utilized between the third to the twenty-first day. The results showed that rapid rewarming cases had better healing than other methods. Grafting was recommendable for the prevention of exposure and necrosis of tendons, underlying fascia, and joints. X-ray examination of the affected part in patients showed that between the third and sixth months some irregular lytic areas appeared in bons which were more related to the depth of injury than the method of thawing.

9. Wilson, R., et al., *Death on Denali.* West J Med, 1978. **128**(6): p. 471-6.

This paper provides a report of deaths in climbers to Denali from 1903 to 1976, moreover, an analysis of fatalities, injuries, and illnesses in 1976. Between 1903 and 1975, The rate of death among climbers on Mount McKinley (Denali) and Mount Foraker in Alaska was about one percent. In 1976, ten people of 587 mountaineers (1.7 percent) died, but this rate of death was not higher than in previous years significantly. There were 18 cases of severe frostbite and 20 cases of mild frostbite. Many severe frostbites were freeze-thaw-refreeze injuries. 11 severe frostbite cases had involvement of hands and feet; in 5 only the feet were frozen; in 2 only the hands. No important freezing injuries to facial organs (the ear nose) or other parts were detected. Four cases of hypothermia were encountered. Orthopedic injuries included four cases of fracture, one dislocation of a shoulder, and two cases of concussion. High altitude illnesses consisted of seven cases of high-altitude pulmonary edema (HAPE), five of cerebral edema (CE), and six of high-altitude retinal hemorrhage (RH). In summary, 40 of 587 (one of 15), 6.8 percent, mountaineers sustained severe injury or illness and ten (1.7 percent) died on Denali and Mount Foraker in 1976. The death rate (1.7percent) is a significantly high rate of death for a recreational human activity. It is approximately equal with overall mortality-18 per 1,000 (1.8 percent) due to illness and injury among the United States soldiers in wars in this century. However, the rate of fatalities among climbers will be 40 to 50 times greater than soldiers during an actual battle if we consider all these deaths in mountaineers in Mount McKinley National Park happen within a few days or a few weeks whereas deaths in armed force are spread over months or years. It is a considerable loss for a recreational activity.

10. Franz, D. R., et al., *Evaluation of fasciotomy and vasodilator for treatment of frostbite in the dog.* Cryobiology, 1978.**15**(6): p. 659-669.

An experimental study in dogs to investigate the effects of fasciotomy and vasodilator on the treatment of frostbite was done in this study. Severe frostbite was produced in the left rear foot of 26 mongrel dogs by immersion in a -27 to -28°C circulating ethylene glycol bath, to a level of 4.5 cm distal to the tarsal-metatarsal junction. Dogs were divided into four treatment groups and all groups received basic therapy that included rapid rewarming and a 20-min treatment in the water bath(38ºC) every day for 14 days after injury. Six dogs were in the control group and received only basic treatment without additional treatment (group A). Six dogs received vasodilator at the onset of rapid rewarming and daily through gastric tube (phenoxybenzamine HCl) (group B). Six dogs were given a fasciotomy incision at 30 min post-thaw (group C). Eight dogs received both vasodilator and fasciotomy (group D).

Foot volumes, deep foot temperatures, tissue pressures, and tissue loss were measured and compared. There was no significant difference between the vasodilator and control group but there were significant differences between fasciotomy and non-fasciotomy dogs in foot temperature, foot volume, and tissue pressure immediately after fasciotomy. However, a significant difference did not exist in 14-day tissue loss between control and treatment groups.

11. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Frostbite.* Alaska Med, 1983. **25**(2): p. 33-8.

An update for the treatment of frostbite was provided based on observation on 800 frostbite cases to explain alterations and new techniques. The conclusion based on the method of thawing in order from best to worst was: 1) rapid rewarming in water (100º to 106ºF); 2) Gradual thawing at room temperature; 3) delayed thawing with ice or snow; 4) Thawing by excessive heat (120ºF or higher).

Treatment was divided into two parts: 1) before thawing: prevention of trauma to frozen part and thawing in warm water 38º to 41ºC (100º to 106ºF); 2) After thawing: prevention of trauma putting in sterile sheets, whirlpool baths twice for 20 minutes every day at temperature 32 to 35ºC (90º to 95ºF) which contained surgical soap or hexachlorophene or betadine. 5.5 % silver nitrate could be lavaged to decrease pain and infection however the end result was similar to hexachlorophene or betadine. Silver sulfadiazine one percent was applied to prevent scar separation by preventing proteolytic bacterial growth. Escharotomy might be done if eschar limited the digits motions like cast or affected blood circulation. If the extremity was in the frozen state for a long time a condition like anterior tibial compartment syndrome might occur therefore fasciotomy would be necessary. Skin grafts was utilized in the third to fourteenth days the result of skin grafts outcomes was best after rapid thawing. Physiotherapy included digits exercises throughout the day and Buerger's exercise for lower extremities four times a day. Results of surgical sympathectomy done within the first 24 to 48 hours decreased pain, edema, and infection whereas causing early and more proximal demarcation. The use of phenoxybenzamine hydrochloride (Dibenzylene) was particularly effective. The drug was used for vasospasm and appeared to be an effective alpha-adrenergic blocking agent applied for

chemical sympathectomy. Severe pain in freezing injury might be relieved by continuous epidural block for 24 to 48 hours. In the past four years, Biofeedback had been used in patients with unstable vasomotor vascular responses to improve the hand and foot circulation in the post-thaw extremity freezing. Tetanus prophylaxis was recommended if it was necessary and the immunized patient should receive a tetanus toxoid booster.

Besides the basic treatment for freezing injury variety of medications had been utilized for post-thaw complications. The post-injury condition could demonstrate: 1) post-thaw vasoconstriction; 2) freezing injury with arteriovenous capillary thrombosis; 3) freezing injury with severe cellular destruction based on the diagnosis of these complications proper drug could be chosen such as anticoagulants (heparin) vasodilators(priscoline) or hypotensive adrenergic blocking agents (Guanethidin, Reserpine) including sympatholytic drugs (Dibenzyline) probably aided in the initial phase, especially in the absence of deep thrombosis. Plasma volume expander such as low molecular weight dextran used early to prevent, diminish or reverse red cell aggregation in the capillary tree. The use of thrombolytic enzymes was being studied.

12. Mills, W.J. and D. Rau, *University of Alaska, Anchorage-section of high latitude study, and the Mt. Mckinley Project (1981-82-83).* Alaska Med, 1983. **25**(2): p. 21-8.

This article was a report of the Mt. Mckinley Project that was a three-year trial project and was assumed to be continued for two more years. However, this project was stopped in 1983. Some of the important purposes for this project were gathering information about human and cold environments, investigating in prevention and treatment of cold injuries, developing standards of cold injury care. It started in 1981 April in two camps at the 7300-foot level (2225 meters) and a high camp 14300 feet during climbing season (April to July). one of the methods for gathering information was a questioner. This questioner had four parts: demographic material, clothing and equipment, ascending questions and medical issues encountered on the mountain by climbers. Analysis of data collected from 397 climbers in 1982 showed 4% hypothermia 16% freezing injury. 31% of frostbite victims walked on frozen feet from one to seventy-four hours, 59% thawed the frozen part in the mountain,12.3 % had the refreezing injury. Since dehydration had been one of the critical problems in cold injuries, total body water and amount of water loss during physical activity were measured in climbers and personnel on the mountain. This measurement was important for determining dehydration and hypovolemia. In addition, the water content of the head and thoracic cavity was measured by using impedance plethysmography to gain quantitative evaluation of high altitude pulmonary cerebral edema.

Previous clinical experiences with using biofeedback training in patients with an unstable vasomotor response and the warming of after-thaw frozen digits were successful. This gave consideration to investigate the use of this training for the prevention of cold injury especially for military forces in cold climates and combat. Therefore, one of the studies was the development of a biofeedback program on Denali to investigate effectiveness in providing peripheral

vasodilation upon demand to prevent frostbite in extremities. Based on Data gathered from climbers, biofeedback training can be offered in military forces to prevent severe vasoconstriction and cold injury. However, transferring the heat from the core to the extremities can reduce the core temperature so using biofeedback for an extended time can cause hypothermia.

13. Kappes, B. M. and W. J. Mills, *Thermal biofeedback training with frostbite patients.* Circumpolar Health, 1984. **84**(1): p. 83-4.

Frostbite patients could be logical candidates for thermal biofeedback, because the vascular control of their extremities might be irregular or non-existent. This report was a thermal biofeedback training on two frostbite patients besides the basic treatment of frostbite developed by Dr. Mills. The first patient was male age 24 with superficial to deep injury in the right foot digits. Technetium studies indicated adequate profusion throughout the foot and toes. Another patient was a 20 years old male with a deep injury to his right foot. Technetium scan showed a profusion deficiency to the first and second toes. relaxation exercises were instructed to patients to practice twice a day. Relaxation was followed by thermal biofeedback training twice a day for 20 to 25 minutes periods. Instruments included two separate thermistors placed on two different sites. Site A was located in an evident blood flow area close to the injury. Site B was placed on a questionable blood flow area or the line of demarcation. Patients were ordered to practice exclusively at site A to reinforce and improve blood flow to the injured area. The results demonstrated increases in the foot temperatures in both patients due to improvement of blood circulation to the injured area. The increase in site A temperature was accompanied by an increase of temperature in site B the site in which the patient did not receive any feedback. Therefore, it could be concluded the increase of blood flow due to training in site A involved blood flow of site B too. Patterns for Patient B were more irregular and lower than patient A because of the greater severity of injury in patient B.

14. Foutch, R.G. and W.J. Mills, Jr., *Treatment and prevention of cold injuries by ancient peoples indigenous to arctic and subarctic regions.* Arctic Med. Res, 1988. **47**(Suppl.1): p. 286-289.

The authors reviewed the treatment and prevention methods that had been applied to cold injuries by indigenous people. Previous studies of native circumpolar people have demonstrated that there was no significant difference in body response to cold between these peoples and natives from milder climates. Therefore, without significant biological adaptation, circumpolar people were able to cope with extreme cold effects on the body by developing special methods. Medical therapeutics differ greatly between tribal groups. Unfortunately, because of the vastness of the territory and the great distances between their territories study of only a few of these tribes was possible. Serious hypothermia or frostbit was rare among Alaskan Indians, however, freezing was a prevalent and minor problem. The preferred way to deal with cold injury was the prevention of that. They avoided travel during periods of extreme cold and wind. Native clothing and footgear using a layering system are the most important factor for prevention. Sometimes their methods for dealing with a cold injury were opposite whereas A lost Indian never stops or sleeps because he believes if do so would result in freezing to death, Eskimos made a shelter to rest and preserved their strength and warmth until the weather cleared. Athapaskan Indians of interior subarctic Alaska were aware of the dangerous risk of using fire heat for thawing and applied slow thawing by using snow and ice water. In contrast, Eskimos used warm water for thawing and Seal oil, animal organs, such as raw liver and whale blubber, were used to treat a variety of injuries, including frostbite.

15. Kappes, B.M. and W.J. Mills, *A sample of personality profiles of frostbite patients in Alaska 1980-86.* Arctic Med. Res, 1988. **47**(Suppl. 1): p. 243-245.

A report of examinations on 35 patients who sustained frostbite from 1980 to 1986 was provided in this article. Physiological and psychological variables consisted of the injury site and severity, type of activity, hypothermia, previous cold injury, alcoholism, and psychopathological issue. In order to evaluate the psychopathological issue in subjects' personality profiles was obtained for subjects based on the Minnesota Multiphasic Personality Inventory (MMPI). MMPI is a test that compares an individual on specific personal attributes to known clinically diagnosed patients of psychological disorders. These clinical scales include hysteria, hypochondriasis, psychopathic deviancy, paranoia, depression, psychasthenia-anxiety, masculinity/femininity, schizophrenia, mania, and introversion/extroversion. 8 subjects were excluded from the study because of communication problems were not able to answer questions and provide a valid profile. Based on data analysis of 27 subjects (20 male, seven female). Three physiological factors had a significant correlation with amputation including the severity of injury (deep or superficial), previous injury and freeze/thaw/refreeze Experience. there was a strong relation between amputation and three psychological variables: undefined activity, presence of psychopathology, and alcoholism. 50% of all injuries happened during sport and recreation however only 18% of all sports injuries resulted in tissue loss. However, 80% of injuries that happened in the undefined category had severe consequences (amputation). The strongest predictor from physical and psychological factors for amputation based on gender was alcoholism and paranoia for males and previous cold injury and hysteria for females.

16. Mills, W. J., Jr, *Comments on this issue of Alaska Medicine--from then (1960) until now (1993).* Alaska Med, 1993. **35**(1): p. 70-87.

In this article, the author provides a summary of the first Alaskan system of care which was established in 1960, and additional changes throughout the 33 years. Since the first reported series of 51 patients in 1960-61,1026 cases of frostbite have been treated. During this time there have been some alterations in treatment but the fundamental concepts are unchanged. Five initial concepts in frostbite were:1) Avoiding refreezing; 2) Utilizing rapid rewarming; 3) Using whirlpool bath twice daily to prevent infection; 4) immediate post-thaw physiotherapy to restore joint motion; 5) escharotomy and fasciotomy in the existence of evidence of compartment syndrome. In 1983 a summary of the treatment of frostbite provided some new achievements about the treatment of frostbite. this paper emphasizes those new additions and adds new processes which had been studied during the last decade.

Sympathectomy: surgical sympathectomy within the first 24-48 hours in patients with bilateral injury, diminished pain, edema, and infection while there was no further preservation of tissues. Phenoxybenzamine hydrochloride (Dibenzylene) was used for vasospasm and appeared to be effective as an alpha-adrenergic blocking agent could be considered an effective medical sympathectomy. It should be noted, stripping of small vessels in hands and feet is an effective form of sympathectomy that could improve perfusion and decrease pain. However, good effects of sympathectomy and vasodilators, and sympathetic blockade following fasciotomy had been under evaluation.

X-ray changes: it had been observed significant changes in bone and cartilage happen after freezing injury. This change was not apparent at the early stage.

However, radiographic changes appeared in x-ray from six to l8 months, therefore every patient should have a series of x-rays from early to late stages to identify the lesions that were due to freezing moreover x-ray file would help to rule out other diagnoses in the future if those lesions would be discovered accidentally.

Drugs: The drugs used in frostbite injury care were: plasma volume expanders (low molecular weight dextran); vasodilating agents (tolazoline hydrochloride); hypotensive

agents (guanethidine monosulfate, reserpine); hemorheological agents (oxpentifylline); calcium blocking agents (nifedipine); sympatholytic agents (phenoxybenzamine hydrochloride); hemorheological agents (oxpentifylline); calcium blocking agents (nifedipine); thrombolytic enzymes (streptokinase, tissue plasminogen activator TPA); anticoagulating agents (heparin); anti-inflammatory agents such as nonsteroidal drugs,, and acetylsalicylic acid, Ibuprofen; industrial solvent dimethyl sulfoxide -- DMSO). The author recommended whether DMSO should be approved by the Food and Drug Administration as an effective penetrant, useful drugs might be attached to its structure.

Until now, there had not been demonstrated any clear treatment policy for preventing injury due to the formation of oxygen free radicals, damaging neutrophils, or reperfusion injury. The reperfusion injury factors and the role of oxygen free radicals were not clear at that time.

17. Mills, W. J., Jr, *Frostbite and hypothermia--current concepts. 1973.* Alaska Med, 1993. **35**(1): p. 28.

Some historical information about the treatment of frostbite was described in this article. Prior to the Korean War, little information was available to the clinician treating frostbite. Progress in the treatment of frostbite came from experimental studies (Lange, Crismor Qintanella, Fuhrman, Meryman, and others) which considered frostbite as a complex phenomenon including not only vascular destruction leading to gangrene, or mechanical damage to cells by ice, but cells dehydration, protein denaturation, intra and extra cellular biochemical changes. It soon became obvious that one of the early problems was the prevention of infection because the infection can cause tissue loss as much as vascular changes. The other problem was the loss of small joint motion from either immobility or cold arthritic changes in bone even if anatomy was preserved by thawing methods or medical care. Therefore, it could be concluded the poor outcomes for rapid rewarming from the previous researches may have been because of failure to prevent the infection, restore the motion and maintain the circulation. Further advancement was achieved in the treatment of frostbite by Dr. Mundth who introduced low molecular weight dextran for frostbite care.

18. Mills, W.J., Jr., J. O'Malley, and B. Kappes, *Cold and freezing: A historical chronology of laboratory investigation and clinical experience.* Alaska Med., 1993. **35**: p. 89-116.

A historical review of investigations and experiences about frostbite and cold injuries pathology has been described in this article. Based on all investigations through centuries authors summarized the pathology of frostbite in two stages: A) the cooling, supercooling, freezing: this stage begins with vasoconstriction after exposure to cold and ends in freezing. Ice crystals forms in the extracellular space and extracellular osmotic pressure increases. This increase results in the absorption of intracellular water and produces intracellular and extracellular dehydration. As freezing continues, cell membrane injury occurs and permeability of cell wall increases. Endothelial cell injury and separation of endothelium from the internal elastic lamina of the arterial wall happens. B) thawing (rewarming) and post-thaw (vascular stage): three important events occur in this stage: vasodilatation, edema, and stasis. Changes due to reperfusion injury, arachidonic acid cascade, prostaglandins, and thromboxane result in vascular clotting and tissue ischemia. Dr. Mills describes 11 patterns of frostbite facing rescuer: 1) true frostbite, superficial or deep; 2) a mixed injury, immersion (wet cold) injury followed by freezing; 3) freezing, thawing, refreezing; 4) hypoxia, high altitude environmental injury ; 5) freezing superimposed to extremity with compartment compression; 6) freezing following extremity fracture or dislocation 7) hypothermia, associated with extremities freezing; 8) freezing superimposed on small vessel disease (diabetes); 9) freezing injury in children (with epiphyseal necrosis); l0) congenital deformity with superimposed freezing; 11) frostbite with superimposed burns or burn injury with superimposed frostbite. The authors explain four methods of thawing as seen after arrival in the emergency room: 1) rapid rewarming by immersion in warm water (31-41C) degrees; 2) gradual (spontaneous) thawing at the room, tent

or cabin temperature, or in a sleeping bag; 3) delayed thawing, applying ice, ice water, or snowpacks often accompanied by friction massage; 4) thawing by excessive heat ,any heat greater than 48ºC, like car heater, oven heat, hot water, campfire. Unfortunately, less than 20 percent of patients arrive in the emergency room with extremities still frozen.

Dr Mills considers freezing and hypothermia a reperfusion injury like any tissue in an ischemic state (e.g., myocardium in heart disease and surgery) and subject to endothelial injury due to oxygen free radicals, and activated neutrophils. He recommends the oxygen free radical, the activated neutrophil, and other inflammatory and immune responses should be investigated in the future as responsible elements in cold injury.

19. Kappes, B., W. Mills, and J. O'Malley, *Psychological and psychophysiological factors in prevention and treatment of cold injuries.* Alaska Med, 1993. **35**(1): p. 131-40.

The article explained applied psychophysiology as a science that uses bio-behavioral methods to achieve the self-regulation of physiology through learning techniques. Biofeedback training was one of the bio-behavioral methods that was used for self-regulation of peripheral skin temperature for the prevention and treatment of cold injuries. The temperature value could be an indicator of vasodilatation. The average skin temperature on dorsal digital surface at rest for females was 88ºF and for men was 92ºF. Patients with medical history of frostbite, thermal disorders, or distressed individuals had lower extremity skin temperatures between 60º to 70ºF. Most of these patients could increase digital skin temperature +20ºF after ten to fifteen half-hour training sessions (5 to 7.5 hours).

A 20-year-old female patient who had a cold exposure (probably superficial frostbite) history attended with complaints of pain in hands after normal daily cold exposures and painful throbbing and burning attacks every day in winter and summer. In observation, hands' color changed red (vasodilatation), white (vasoconstriction), and blue (venous stasis) within a few minutes. This rapid discoloration pattern was the characteristic of primary Raynaud's. However, in this case, it was called "Raynaud's Phenomenon" or secondary Raynaud's because it was secondary to cold injury. Her finger temperatures ranged from 69º to72ºF when she was offered biofeedback training. She was able to increase the temperature to above 90ºF after16 half-hour sessions. It showed blood vessels attained normal relaxed expansion which could be used in cold challenges as well. The frequency of painful attacks decreased from 2- 3 per day to one or two every two weeks or less as well.

Frostbite and hypothermia

20. Mills, W.J., Jr., *Summary of treatment of the cold injured patient.* Alaska Med, 1973. **15**(2): p. 56-9.

This article provided a short note about the treatment of hypothermia and a new update for frostbite. Dr. Mills explained rewarming of the hypothermic patient in the warm water bath, 32 to 38ºC (90º to 106º F) would be alert and rational rapidly. However, rapid rewarming without supervision could result in very fast metabolic acidosis and death by ventricular fibrillation in less than one to three hours in rapid rewarming.

Frostbite treatment prognosis differed based on the method of thawing. In order of prognosis from best to worst: 1) rapid rewarming by immersing in water 38º to 44ºC (100º to 112º F); 2) gradual thawing at room temperature; 3) delayed thawing or thawing by using ice and snow; 4) Thawing by excessive heat (120ºF or higher). Thawing by rapid rewarming in warm water is the best choice for thawing because of the greatest tissue preservation.

Treatment of frostbite was classified into two parts: 1) before thawing: prevention of trauma to frozen part and thawing in warm water 38º to 41ºC (100º to 112ºF) 2) After thawing includes daily whirlpool baths, Physiotherapy (bedside extremities exercise and Buerger's exercise for lower extremities), escharotomy (if it was needed), antibiotics (based on culture results). Two new modalities were discussed: 1) lavage of 5.5 % silver nitrate can decrease pain and infection however the final result is similar to hexachlorophene or betadine; 2) If the extremity was in the frozen state for a long time a condition like anterior tibial compartment syndrome might occur therefore fasciotomy would be necessary.

21. Mills, W.J. and R.S. Pozos, *Low temperature effects on humans.* Encyclopedia of Human Biology, 1997. **5**(2): p. 383-401.

The definition and pathophysiology of hypothermia and frostbite has been reviewed in this article. Hypothermia is defined as a 2ºC decrease in rectal or core temperature. Hypothermia begins at 35ºC clinically, and it may go as low as 18ºC. Hypothermia has been categorized into primary, where hypothermia happens in a body with normal thermal regulation due to exposure to overwhelming cold, and secondary hypothermia is a result of a mild or moderate cold exposure to a body with abnormal thermogenesis. In secondary hypothermia, the physiological responses to cold are not normal and effective. In normal thermoregulation, the first response to the cold is goose pimples. Shivering and the feeling of numbness happen in greater cooling. At approximately 35ºC incoordination and stumbling happen and when the temperature drops to 34.4ºC, dysarthria occurs, and the victim talks with a mouthful of mush. When cooling continues at 32.2º to 31.1ºC the person slides to the semi-comatose phase. Various victims demonstrate bizarre behavior patterns including undressing. finally, at 29.4ºC temperature, the victim slides to the metabolic icebox.

In cold exposure, when heat loss is sufficient enough to form ice crystals in the extracellular spaces frostbite occurs. The two important variables in freezing are duration of exposure and temperature. At very high rates of freezing, ice crystals form throughout the tissues, usually intracellular. At slow rates of freezing ice crystals form in the extracellular spaces. Terrestrial freezing rates are usually in the slow-freezing range; therefore, extracellular ice crystals are the major concern for frostbite study. Present knowledge demonstrates that the pathophysiological changes of frostbite occur in two stages. The first stage is the cellular stage, wherein cellular changes occur during cooling and freezing such as structural damage,

dehydration, PH changes, protein denaturation, etc. The second stage of injury happens during the thawing and in the post-thaw stage (the vascular injury) which results in thrombosis, ischemia, necrosis, and gangrene.

Hypothermia

22. Mills, W.J.J., *Accidental hypothermia: management approach.* Alaska Med, 1980. **35**(1): p. 54-6.

This article includes information from a historical review of fifty cases of hypothermia in Alaska and a management approach to the treatment of hypothermia. Their age varied from 24 to 90 years and their temperature ranges were from 36º to 23ºC however, a large number of these patients had a temperature of 34.4ºC. They were given heat by various methods (slow, rapid, controlled, uncontrolled, etc.). Four deaths happened, apparently due to cardiac failure methods of rewarming were not mentioned. Most of the victims were dehydrated, demonstrated mild to severe acidosis with evidence of hyperkalemia either during or after warming the degree of consciousness was correlated with the level of hypothermia. It was obvious the most important part of the treatment of hypothermia was control of metabolic and cardiac and chemical issues which appear during and after rewarming. Duration of this control could be up to three to eight hours in slow warming methods like spontaneous warming or short thirty minutes to two hours in rapid rewarming methods. Treatment included two important elements 1) rewarming including rapid rewarming 32º to 41ºC (90º to 106ºF) spontaneous warming, peritoneal dialysis, etc. 2) physiological control including airway control, restoration of electrolyte imbalance, correction of dehydration, correction of acidosis and alkalosis, restoration of renal function, preparing multiple intravenous access. When the patient was under total system control the method of rewarming was not important and professionals could use their familiar method.

The purpose of treatment was to restore a normal blood volume and overcome the dehydration, restore acid-base balance, restore proper electrolyte balance and prevent a post rewarming hyperkalemia, achieve a normal renal flow, and prevent cardiac arrhythmias and

arrest. It should be considered a cold heart at very cold temperatures is not responsive to defibrillation procedure and electroshock and the heart may not be at a true cardiac arrest just the heart is in a very delayed metabolic response to severe cooling therefore it is not reasonable to utilize chest massage or electrostimulation for a heart is unable to respond that stimulation due to cooling.

Results showed that from fifty cases 14 cases 27.5% were rewarmed by warm pads, blankets, heated moist air under total system control all survived. 17 cases 33.3% were warmed in a tub at 100º to 106ºF including 10 patients with deep frostbite in extremities all survived.

23. Samuelson, T., et al., *Hypothermia and cold water near drowning: Treatment guidelines.* Alaska Med, 1982. **24**(6): p. 106-11.

The guideline for the treatment of hypothermia and cold water near-drowning starts with a general consideration. The first evaluation like other injuries consisted of A) airway B) breathing C) circulation, however, in the setting of cold injuries the rectal temperature is one of elements and it would be D) The rectal temperature should obtain by "low reading" thermometers and using regular thermometers can be dangerous in this field. Since the low reading thermometer usually is not available the guideline is not prepared based on the measured temperature. Basic treatment for hypothermia for the first responder includes: 1) treat gently 2) remove wet clothing 3) prevent further heat loss at the core by insulating the patient from cold 4) add heat; it can be external warm packs on head neck chest and groin or it can be breathing warm moist air or oxygen 5) avoid rubbing 6. refrain from alcohol or coffee 7) avoid warm water bath 8. warm drinks just allowed after total consciousness. If any of the following symptoms or signs are observed in hypothermic patients, they will be considered severe hypothermia: temperature 32ºC or less absence of shivering, depressed vital signs, altered consciousness, and accompanying with an injury or illness. If patients do not have any of these symptoms they will categorize in moderate to mild levels.

All severe hypothermia patients should be transferred to the hospital after basic treatment if there is not any chance to get hospital just warm the patient. If the patient with severe hypothermia does not have vital signs and you can not detect any pulse and respirations, should start CPR (mouth to mouth is better than bag/mask breathing). However, there is some controversy about applying CPR for a very cold heart but until getting more information about its controversy CPR is recommended for all pulseless apneic patients.

Based on cold water near-drowning protocol, anybody who submerged under water long enough to lose consciousness or require CPR and duration was less than one hour should be transferred to the hospital. In near-drowning cases, respiratory and coagulation problems are more important than hypothermia because most of the time water temperature is around 30 rewarming if is necessary should do gradually. Resuscitation should be applied for victims who had less than one hour or uncertain duration of drowning. There is not any difference between salt or fresh water near-drowning treatment and these principles are for any near-drowning victim in cold or warm water. However, survival in cold water for long submersion of more than 6 minutes is much more than warm water. Anybody who encounters a near-drowning victim (general public or medical professional) in the first place should clear the airway, CPR must be started then other associated injuries should be assessed. Heimlich maneuver is prohibited in these patients.

24. Mills, W.J., Jr., *Summary of treatment of the cold injured patient. Hypothermia.* Alaska Med, 1983. **25**(2): p. 29-32.

Hypothermia features and treatment has been reviewed in this article. Homothermic control is unstable or lost at a temperature lower than 33ºC (94ºF). Many hypothermic patients are dehydrated and hypovolemic with mild to severe acidosis and evidence of hyperkalemia either after or during rewarming. The degree of consciousness has been correlated with the level of hypothermia. Some of the characteristics of hypothermia are lowered core temperature, dehydration, anaerobic metabolism, metabolic acidosis, renal dysfunction, fluid shifts, electrolyte imbalance, and consciousness. Treatment includes: 1) rewarming 2) physiological control (airway, monitoring heart, blood gases, electrolytes). Therefore, under total physiological control, the method of rewarming and the depth of hypothermia (even to the level of 21.1-23.8ºC) is not important. Several methods for warming can be applied: A) external passive warming warm shelter, dry clothing, and blanket, insulted mats; B) external Active warming warm blankets warming cradles radiant heat rapid rewarming in tub or whirlpool bath; C) internal (intracorporeal) warming warm enemas, gastric lavage, inhalation warm moist oxygen (38 to 43ºC) or warm intravenous solution 38º to 41ºC; D) internal (Extracorporeal) warming: peritoneal dialysis hemodialysis. Whereas further cooling can result in death from vital organs cooling in the victim who may be in the metabolic icebox, uncontrolled warming can result in death due to uncorrected acidosis or increase of potassium or hypovolemic shock.

25. Mills, W.J., *Field care of the hypothermic patient.* Int. J. Sports Med., 1992. **13**(Suppl. 1): p. S199-S202.

The care should be provided by the first responder for the hypothermic victim in the field is discussed in this article. At the first step, the victim should be evaluated by the responder to assess the hypothermia state. Since a low reading thermometer is not available it is important to estimate the state of hypothermia by signs. The first response to the cold is goose pimples. Shivering and the feeling of numbness happen in greater cooling. At approximately 35ºC incoordination and stumbling happen and when the temperature drops to 34.4ºC, dysarthria occurs and the victim talks with a mouthful of mush. when cooling continues at 32.2º to 31.1ºC the person slides to the semi-comatose phase and finally in 29.4ºC temperature, the victim slides to the metabolic icebox. The first responder who faced a hypothermic victim should attempt to remove the victim from the wind or locate into a tent, shelter, snow cave, slip trench, snow or windbreak. the patient may be placed in a sleeping bag if it is available. all wet clothing should be removed and attempted to clothe the victim in dry clothing. If the victim is conscious and can swallow normally so warm fluids help to warm. The rescuer should prevent heat loss but not add heat rapidly. Adding heat rapidly in the field without physiological control may result in cardiac arrhythmias due to imbalance electrolysis which are not treatable in the field. In any event, the victim with no signs of life the general rules for shelter and dry clothing still is applicable. Moreover, some closed-chest manipulation and mouth-to-mouth resuscitation should be tried and transported to a medical facility without danger to the rescuer. The patient is dead only when warm and dead however this may not be possible in an isolated environment.

Non freezing cold injury (Immersion injury)

26. Mills, W. J. and W. I. Mills, *Peripheral non-freezing cold injury: immersion injury.* Alaska Medicine. **35**(1): p. 117-28.

The Immersion injury is described as a peripheral non-freezing cold injury that is due to salt or freshwater exposure, usually at low temperatures near, but not at, freezing levels. When Immersion injury happens, extremities are "numb" and swelled, the skin color first is "red" in appearance, then changes to pale or mottled blue or black and cramping of calves. After rescue and warming, three "stages" or clinical time zones were described; 1) The pre-hyperemic (post initial warming) stage feet are numb with extreme edema and swelling may progress from the extremities to above the malleoli. This stage can last from a few hours to many days. 2) The hyperemic stage is one lasting as long as six to ten weeks. In this stage, the anesthesia is eventually replaced by tingling, aching, pain, and intermittent throbbing. Extremities color can change to cyanosis Intermittently; blister formation and gangrene may occur. 3) The post-hyperemic stage may last for weeks and even months, and in some cases, for years. in the post hyperemic stage, inflammation reduces, vascular tone recovers, and skin temperature decreases. The extremities are cold-sensitive with Raynaud's phenomenon or digital blanching.

Complete Immersion injury in the Alaska series was seen in 105 of 1.,282 cold injured patients. Immersion injury was described by many scientists as a disease of nerves and muscle, however, in this group microscopic and tissue examination on tissue samples from fasciotomy or partial amputation found many of the changes in blood vessels. Therefore, acute and later treatment must include restoration of circulation. Treatment includes: a) treatment of compartment syndrome if indicated, by applying fasciotomy to release the tissue from pressure; b) use of medications that improve vessel dilatation and loss of sympathetic effect to help in

decrease edema and reduce edema pain; c) ordering drugs that relieve severe pain as in epidural blockade; d) the prevention of infection by applying the whirlpool and gentle care of the extremities.