BLAIR

CLINICAL HYPOTHERMIA

Clinical Hypothermia

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PREFACE

Few men make themselves masters of the things they write and speak.

John Selden

Hypothermia has been accorded the accolade of a "modern wonder" of medicine in the twentieth century. Nothing could be farther from the truth. The limitation of hypothermia to a narrow field is the reflection of contemporary "popularity" of a clinical problem. The net result has been a "Johnny-come-lately" of its potentials which were proposed almost 150 years ago. Hypothermia in recent years has indeed become an extremely important tool in cardiovascular surgery. Actually, this amazing modality was originally designed for the management of ills not amenable to surgery. In more recent years (in the interminable cycles of rediscovery) recognition has been granted to the possible advantage of hypothermia as an adjunct to therapy in a variety of disease states.

The avidity with which interested members of the professional community read reviews on "new" developments in medicine must be tempered with the controversies, the inadequacies, and the bias of such documents. There can be no such thing as a hypothermia dogma because there is not enough known about it. There are several good reasons for this. First, clinical trials often do not permit controlled investigative analyses. Second, the induction of hypothermia in a homeothermic mammal (to which peculiar biologic structure dogs, apes, and human beings belong) touches the very roots of mystic fundamental functional mechanisms, about which much must yet be learned. Third, there is an extremely complex and magnificent device known as the temperature-regulating mechanism, the precise workings of which continue to elude total explanation. Fourth, hypothermia research is probed by an almost staggering multiplicity of experimental conditions. This intellectual diversity, added to the limitless inherent variants peculiar to biological research, permits rather free excursions into theory and study. Reducing biologic data to a simple ABC has a mesmerizing appeal. Scientific temperance and common clinical horse sense are needed restraints in extrapolation to the human problems.

Nevertheless, because of continued interest and, more important, the increasing use of hypothermia in people, this document has been prepared to assist in assessing hypothermia and in outlining its possible role in medicine.

The underlying theme of this monograph is the application of hypothermia to the sick patient on the basis of a fairly reasonable physiologic rationale. By the nature of circumstances previously mentioned, it is obvious that some compromise of this theme is necessary. A principal modification in applying hypothermia is the incorporation of a healthy dose of clinical judgment. However, clinical judgment alone, in the absence of some understanding of changes induced by hypothermia, not only mitigates against a healthy intellectual medical environment but has had, and will have, disastrous consequences. The two ingredients required for the clinical use of hypothermia, therefore, are a background of physiologic changes and a continued adherence to established medical principles in the management of the sick patient. The fundamental media of exercise of these constituents lie in the indications for the use of hypothermia, how long to use it, how to induce it, how to manage the patient, and, finally, how and when to rewarm the patient.

The author's treatment of physiologic changes produced by hypothermia should not be construed as gospel. The variety of experimental conditions and the limited amount of research done on human beings do not permit a concise, specific, and unquestioned elaboration of hypothermic influences on the homeotherm. As much as possible, reference to clinical physiology will be made, but for the most part it will be necessary to discuss changes observed in animals, in particular, the dog, and to extrapolate some of the findings to the human being.

The proverbial friendship between man and dog often bears little context to a physiologic relationship, but in the proper perspective some aspects may be acceptable. Reported functional changes come from two sources: the work done by the author and associates at the University of Colorado, at the United States Army Medical Research Laboratory at Fitzsimons Army Hospital, and at the University of Maryland and the scientific literature. The discussion of the clinical application comes primarily from experiences at the University of Maryland, where hypothermia has been used in many instances other than cardiac surgery. An attempt is made toward developing a classification of hypothermia based on physiologic changes; to identify those clinical states for which hypothermia may be of potential benefit; to describe technical procedures in cooling and the maintenance of the patient under hypothermia; to enumerate complications secondary to hypothermia; and finally to evaluate the rightful place of hypothermia in the practice of medicine. Hypothermia has tolerated quite admirably the cycles of receptivity and rejection foisted upon it by a rather fickle medical profession. It will be emphasized time and again in this document that hypothermia is not a gimmick and, above all, is not a substitute for any form of treatment. Clinical hypothermia is an adjunct and as such, another tool. The ratio of risk to the patient is manipulated not by the cold itself—but by the physician.

Many individuals contributed directly and indirectly to this book. Special note is made of opportunities for initial studies in hypothermia at the Halsted Surgical Laboratory at the University of Colorado Medical Center. The author's period of service at the United States Army Medical Research and Nutrition Laboratories, Fitzsimons Army Hospital, Denver, Colorado, permitted unexcelled media for further investigations. Continued research and clinical programs in the Department of Surgery, the University of Maryland, provided much of the material and stimulus for completion of the manuscript.

The author's research and clinical investigation in hypothermia have been made possible through grants from the office of the Surgeon General, U.S. Army Medical Research and Development Command and the U.S.P.H.S. National Institutes of Health. From the latter, in particular, an award in the Career Research Program has aided research in several important respects.

The talents of Thomas Stevenson of the Medical Art Department and George Henning, my assistant, have greatly enhanced the presentability of the manuscript. The manuscript finally emerged through the patience and labors of my secretaries, Miss Kay Little and Mrs. Norma Norman.

Emil Blair, M.D.

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WHAT IS HYPOTHERMIA?

"The only thing that is new is that which is forgotten."

Mistress to Louis XIV

Historical Note

Hypothermia is a product of the art of rediscovery, a principal characteristic of medical research. The earliest available records in history attest to the use of cold in various forms.[16,27] In 1772, Robert Boyle had proposed possible benefits from cold.[21] James Currie, a Scotch surgeon, in 1797 astounded the Royal College of Surgeons in London with his report on using cold to lower body temperature.[7] This was the first truly scientific document on hypothermia. Due credit was given to a Dr. Wright, who 30 years earlier, while cruising in the Bahamas, used cold as treatment for a tropical disease. It seems that Dr. Wright, in the service of the British Royal Navy, was the only member of the ship's company to be afflicted with one of the pestilences natural to the Bahamas in the early eighteenth century. After spending several intolerable days in the ship's hold, Dr. Wright ventured topside during rather heavy seas. While standing on the deck, the unhappy physician was engulfed by a wave which broke over the vessel. He was struck by the immediate improvement in his febrile state. After the seas had calmed, he instructed the sailors to douse him with the sea water for several days. In a short time his fever had totally abated, and he was completely cured. This particular experience may well not have been hypothermia but merely a glorified sponge bath. In any event it was most effective and led Dr. Currie to institute cold for the treatment of diseases customarily found in a seaport city (Liverpool) in the period of approximately 1776 to 1797. Furthermore, this astute gentleman recorded temperatures below 94° in normal subjects uncomfortably immersed in a tub of brine.

Energetic enthusiasm and the lure of a new magical means of treatment are not limited to the modern physician. A wave of excitement swept through the continent; and for about 30 years, hapless victims of a multitude of physical ills were dumped into a tub of brine twice a day for several weeks. The activities, except for the researches of Dr. Currie, were primarily devoted to clinical or empirical use of cold. This period may be called the "first clinical" or "early period" of hypothermia. The period of deluge receded, inevitably. The ebb of interest in clinical hypothermia coincided with the birth of one of the most magnificent periods in medical history, the golden era of physiology, which began in the late eighteenth century and blossomed in the nineteenth century. Hypothermia, although partially abandoned as a clinical tool, was recognized as an extremely interesting research medium and was used extensively. The body of research during the early part of the nineteenth century was done primarily by British and French investigators and limited mainly to studies of reflex mechanisms. Claude Bernard in 1855 noted the presence of hyperglycemia during hypothermia.[2] Later when Walter Cannon employed local gastric cooling, he recognized a reduction of gastric motility and secretion.[6] In recent years, this physiologic sequel of cold has been used clinically in gastrointestinal problems. The central nervous system was believed by Bernard to be irreversibly damaged below 20°C. Larrey, physician to Napoleon, observed that exhausted soldiers succumbed to cold quite easily.[24] Reports of accidental cooling in the human being appeared with increased frequency in the latter part of the nineteenth century. Reinke and Nicholison reported on drunkards surviving temperatures as low as 20°C.[9] Schafer, from 1868 to 1894, cited numerous incidents of temperatures of 30 to 24°C in psychotics and alcoholics, some of whom recovered.[25] Edwards in England in 1824 noted that newborn pups and kittens tolerated hypothermia much better than did adults.[13] Simpson and Herring, in 1905, reported on the effect of cold narcosis on reflex activity in the homeotherm, observing that the heat-regulating mechanisms began to fail at around 25°C.[28] This early observation has been confirmed a number of times. In 1914 Markwalder and Starling described their series of experiments on myocardial function and elaborated upon the effect of cold on ventricular activity.[22] This second era of hypothermia may be termed essentially the "physiologic era." It extended up to about the end of World War I. Toward the latter part of the nineteenth century a number of reports on clinical use of hypothermia appeared.[1,32,33]

In 1938, Smith and Fay began their epoch-making experiments in hypothermia and clinical application in terminal cancer and neuropsychiatric disorders.[29] Dill and Forbes, in 1941, reported the first respiratory changes in hypothermia in these patients; subsequently Talbot demonstrated some of the circulatory effects.[10,31] This may be termed the "modern era" of hypothermia. This period also witnessed the work of McQuiston and of Bigelow and his group[3,23] and the introduction of the term *artificial hibernation*, from the continent, particularly espoused by Boerema, by Dundee, and by Laborit in which drugs were used to depress sympathetic nervous system activity and permit total body cooling.[5,12,18] This modern era of hypothermia may well be divided into two additional phases: The cardiovascular phase began in 1953 when Lewis and Tauffic performed the first open-heart surgery, closing an interatrial septal defect (secundum) under hypothermia which was achieved by surface-immersion cooling.[19] This procedure was popularized by Swan.[30] It is of particular interest that hypothermia was advocated not just for cardiac surgery, but for poor surgical risks and for other general surgical problems.[20,30] However, for several years after 1953, the emphasis was directed toward cardiac surgery, and the general use of hypothermia was apparently in abeyance. While hypothermia was the current sensation, another brilliant step was in the making. Pump oxygenating systems were developed by Gibbon, Björk, Delorme, and Gollan.[4,8,14,15] This led to an abandonment of hypothermia in some quarters. Among the reasons given for the ready abandonment were the high incidence of fatal ventricular fibrillation and the short permissible time for surgery. Critical matters regarding level effects of temperature upon the heart and other vital organs had to wait for clarification. The eventual combination of extracorporeal circulation and hypothermia facilitated refinement of pump-oxygenator systems and more adequately defined the role of hypothermia, whether alone or in conjunction with the pump. Individuals responsible for this are too numerous to mention. Profound hypothermia had been advocated for many years by the indefatigable Gollan, but fell on unhearing ears until very recently when Sealy and his group at Duke University and Drew in England demonstrated successful clinical application of profound hypothermia.[11,26]

In 1956, Lewis reported on the use of hypothermia for extremely ill patients and several scattered reports appeared in the literature on the use of hypothermia for medical and surgical problems.[20] At the University of Maryland, beginning in 1958, the study and application of the broader range of hypothermia were begun and continue to the present date. The modern era of hypothermia, then, may be divided into the cardiac surgery era beginning in 1953 and the general utility era beginning in 1956.

Definition of Hypothermia

Hypothermia is the lowering of the body temperature of the homeotherm below 35°C. It is *not* a number of things. It is not artificial hibernation. To induce hibernation in a homeotherm is impossible. Only hibernators, which naturally hibernate in winter, can be artificially hibernated in the summertime. This is true artificial hibernation but does not completely resemble natural hibernation. Hypothermia is not refrigeration. It is quite possible to convert the homeotherm into an ice cube, but clinically not desirable. Suspended animation has been reported by the workers at Mill Hill in England. However, there have been no survivals. It is unlikely that a true state of suspended animation can be developed in the homeotherm under the circumstances with which we are presently familiar. Under deep hypothermia below 10 to 12°C activity of the heart ceases. It is possible then that the heart undergoes suspended animation and thus the homeotherm may experience "regional" suspended animation.

All these definitions fail to pinpoint hypothermia in the homeotherm accurately. The fundamental reasons lie in the difference in characteristics of the temperature-regulating mechanism in the biologic species. The nearest the homeotherm may come to its innate reaction to low temperature is that of poikilothermy (after a stabilized hypothermic state is reached). This possibility has been demonstrated by Keller in some admirable experiments in the dog.[17]

It has been customary in describing the hypothermic state to refer to this simply as hypothermia. Generally, the individual in the hypothermic state is not in true hypothermia. Any attempt at reduction of the temperature below the accepted normal limits is met with the mobilization of some rather powerful forces, the nature of which are not fully understood at the present time. The primary, and most obvious, manifestation of this effort to resist lowering of body temperature in the human being is shivering. This is an exaggerated skeletal muscle activity, and although it does not account for all the heat production, it does account for a significant proportion of the production at rest and for practically all during stress, especially upon exposure to an external cold environment. The shivering is a highly undesirable feature for several reasons.

1. The enormous increase in heat production (manifested by tremendous increase in oxygen consumption) will not permit the smooth rapid lowering of temperature to the level desired. This particularly is true in attempting to lower the temperature to fairly deep levels.

2. Excessive shivering may induce cardiac arrest or fibrillation.

3. Cold exhaustion may supervene and prove lethal. It is necessary, therefore, to depress, or to abolish completely, this portion of the heat production mechanism. This is usually accomplished clinically and experimentally by a variety of anesthetic agents often in conjunction with curare or curare-like drugs. The physiologic effects of these drugs especially on circulation, ventilation and upon adrenal hormone production have been well established.

Clinical hypothermia is a state of adjustment to cold modified by drugs. The situation is even more complicated when, as a result of the reduced elimination and/or conjugation of anesthetic or other drugs by the liver and by the kidneys due to cold, the drug effects are not at all as predictable as under normothermic circumstances. Consequently, it would be more accurate to refer to modified hypothermia and not just simply to hypothermia. The only exception is when attempts are made to cool without the aid of anesthetic agents. This has been particularly true in hypothermia studies in small animals and in the use of hypothermia in extremely ill patients, whose reflex mechanisms are so depressed that very little if any shivering occurs upon introduction of the cold environment.

The failure to designate specific levels of cooling (except perhaps in the profound depths) has led to great confusion and misconceptions, with regard to both the utility and the hazards of hypothermia. It is readily apparent that the physiologic alterations would be directly proportional to the depth of the cooling. Another denominator is the temporal factor. In experimental work, for example, little attempt has been made to establish the steady state or stabilized hypothermia. In many studies, animals are cooled to a particular level and once the desired temperature is reached the experiment is executed. Then the animal is rewarmed. Exceptions have been the works of Fisher, of Horvath, and of Blair. Clinically, when hypothermia is used for correction of cardiac defects, the patient is at the projected level of hypothermia for only a brief period. This patient only skirts the lower temperature. Gradients are still changing dynamically, as are oxygen uptakes by various organs. Enough time has not elapsed to permit physiologic stabilization.

Hypothermia in a homeotherm is a potentially risky state, regardless of the manner in which the cooling is induced. The more moderate the level of cooling, the longer the period of safety at that level. The deeper levels of cooling invite greater hazards.

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2

PHYSIOLOGY OF HYPOTHERMIA

The white cold virgin snow upon my breast
abates the ardour of my liver.

The Tempest, Act IV, Scene 1

Temperature Regulation

Man is warm-blooded. He belongs to the biologic thermal stratum known as homeothermy. This means that normally his body temperature is kept within rather narrow limits regardless of change in the temperature of his environment. The regulation is precise and is mastered by a complex neurohumoral device not fully clarified as yet. Familiar animals under a similar control include monkeys, dogs, cats, and rabbits. Mice and rats, while homeothermic, are way down the scale and react to temperature change in a quantitatively different fashion, tolerating cold far better.

The thermostatic control in man consists of two integral units which operate through both positive and negative feedback systems. One unit is physical regulation, consisting of a nervous system and the circulation.[91,86] The second is chemical and is concerned only with heat production. The unit here includes hormonal components: (adrenal glands, thyroid) and neuroeffector chemical substances.[185] The nervous system is a relay component telegraphing temperature changes at the skin from the electronic outposts (Krause and Ruffini thermoreceptors).[8,28] The messages are flashed to the communications centers through a series of relay stations. These communications centers are located in the hypothalamus.[26] Here the messages are interpreted and an integrated response is initiated either to increase heat loss, to conserve heat, or to actually increase heat production. These responses come from either the anterior hypothalamus in which the heat loss center is located or the posterior hypothalamus, the locale of the heat conservation center.[185] This center, when activated, sets in motion the machinery for increasing heat. This is done by (1) vasoconstriction of skin vessels, reducing blood flow and, hence, heat loss, (2) vasodilation of muscle vessels, increasing perfusion for the skeletal muscular role in heat production, and (3) stimulation of the endocrines to increase metabolic rate and hence produce more heat. The anteriorly located center initiates generalized vasodilation to increase

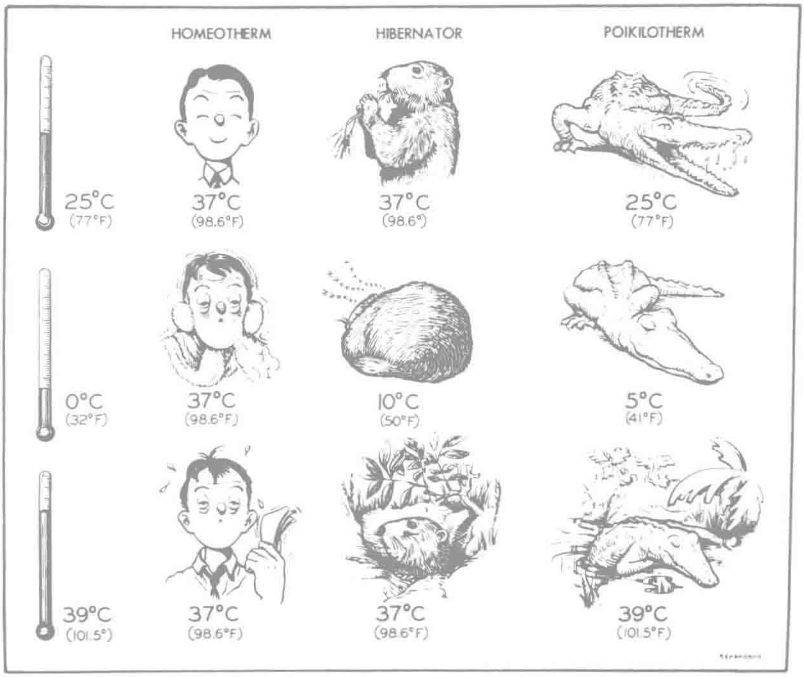

Fig. 1. Man retains a normal body temperature regardless of outside temperature. With cold the hibernator goes into a deep sleep from which he can be roused with subsequent rise in body temperature. Hypothermic man does not become an artificial hibernator, but may assume some characteristics of poikilothermy.

heat loss in response to warm stimuli. From this description the important role of the circulation is evident.[70,183] Perfusion of an organ to a large measure dictates the temperature of that organ. This function is exploited in cooling a patient with pump-oxygenator systems with a rapid heat exchanger, in which the circulating blood temperature is drastically lowered before its return to the patient. In addition to central neural control, the skin vessels react directly to temperature stimuli, constricting with cold and dilating with warm exposure.[21,70,176] The known endocrine responses include the thyroid and adrenal glands.[73,86] In recent years increasing importance has been attached to noradrenalin as a mediator for increasing heat production, especially in cold-adapted situations.[171]

When a human being is exposed to cold, the Krause thermoreceptors in the skin are stimulated because of an increase in temperature gradient between the skin and the core (deep body zone). An increase in this gradient occurs when the skin becomes cooler. A reflex vasoconstriction of skin blood vessels from direct cold effect enhances the increase in the gradient.[289] The signals received by the Krause antennae are picked up by a preamplifying system, the dorsal roots of the spinal cord. Transmission speeds along the spinothalamic tract to the thalamus and reticular system for integration and amplification. The broadly increased signals are then relayed to the control center in the hypothalamus where they are interpreted. Cool blood is also a potent signal here.[26] The machinery for maintaining normal body temperature in the cold environment is set into motion. Activation is through at least three modules. A switch is automatically tripped and the sympathetic nervous system goes into

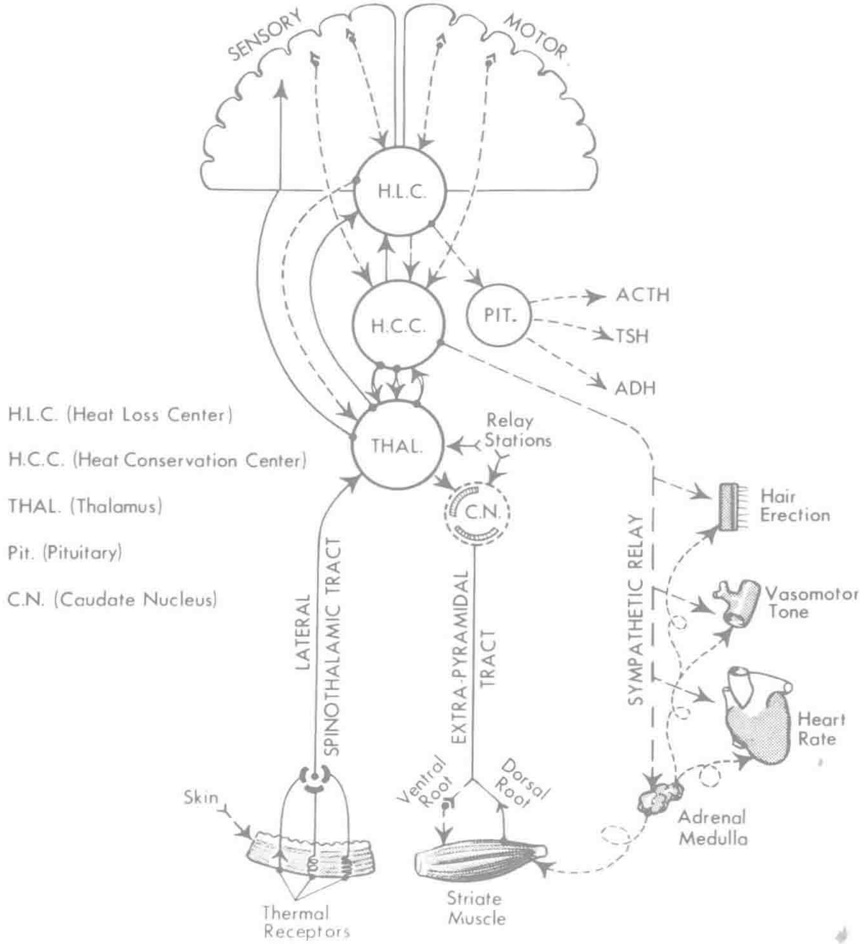

Fig. 2. Schema of thermoregulation (see text for details).