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Table of Contents

INTRODUCTION

At the Ninth Annual Assembly of the Omaha Midwest Clinical Society in October, 1941, Dr. Harry E. Mock, assistant professor of Surgery at Northwestern University, and a surgeon of national repute, presented a method for emergency treatment in traumatic wounds of the extremities. This new method, still experimental in current use, proved to be an adaptation of the century old application of cold in disease processes. In an effort to better understand the theory and thus the practical application of Dr. Mock's presentation, a study was inaugarated to investigate cold therapy in the practice of medicine. Preliminary survey revealed that to report on the multitudinous number of uses to which cold has been put in therapeutics would involve a comprehensive study of the total literature as regards therapy, not only in the general practice of medicine but all of the specialties as well. Therefore, this thesis concerns primarily an elucidation of the mechanism whereby cold effects the body and some of the more recent therapeutic agencies which employ cold as the principal component.

With the recent reinovation of cold as a therapeutic agent of major import, there has arisen some discussion as to terminology which would most accurately describe the various techniques. At the present time this terminology is in a state of flux so that there results some confusion. Cryotherapy or crymotherapy refers only to the general use of cold as a therapeutic agent. Recently there has been suggested hypothermy as a more descriptive term.

Kovacs (71) believes that a further classification should be included. Medical, to include both generalized and local reduction of temperature, and surgical, to denote the various freezing techniques in preparation for local incision. Refrigeration is loosely used for reduction of temperature, either general or local, freezing has suffered the same laxity of interpretation, and artificial hibernation has been used to denote a generalized reduction of body temperature. While many of the experiments still adhere to descriptive terms they originally employed, it seems as though Kovacs' suggestion and classification is the most accurately descriptive and therefore is beginning to be more extensively used.

As far as can be discerned, the introduction of two new hypotheses for the use of cold have arisen in the United States. Frederick M. Allen in New York started in 1929 to scientifically study the effects of temperature on constricted limbs. This pioneer work culminated in the method of treatment which Dr. Mock presented at the Midwest Clinic. In Philadelphia, Temple Fay and Lawrence Smith, after preliminary scientific observations and experimentations finally utilized cold as a therapeutic agent in the treatment of cancer in October of 1936. With these three men as starting points experimentation has radiated into the various branches of medicine in an effort to realize the full potentialities of cold as a therapeutic agent. The results of the investigations are being currently published and indications are that the aforementioned potentialities are far from exhausted. Thus, while this paper will endeavor to summarize what has recently

been accomplished, the final chapter of the use of cold in the practice of medicine awaits comprehensive research.

HISTORICAL SUMMARY OF CRYOTHERAPY

The use of cold to ease the pains of man undoubtedly has its origin in the primitive epochs when he first used implements. Although no records of this kind have been as yet found, one can imagine this primitive man cutting and bruising his hand or finger and then bathing the injured part in cool water to ease the bleeding and pain. The earliest written evidences of the therapeutic use of cold are found in the ancient histories of the Assyrians and Egyptians. The ancient Greeks, Persians and Hindus also used cold water in the practice of medicine in their ancient civilizations. From the other side of the world there is found in a Chinese record dated several centuries before Christ, a prescription for one hundred affusions in cold water, each to be followed by wrapping in a linen sheet. (68) This simulates the modern practice of the wet pack which is extensively used.

Grecian mythology speaks of the benefits to be derived from cold baths and in the Spartan civilization the healthful attributes of cold water must have been known for there were laws making cold baths obligatory. The organization of thought concerning the therapeutic use of cold water seems first recorded by Hippocrates, to whom so many other things are accredited. Hippocrates, the Father of Medicine, apparently had a rational understanding of most of the principles of cold and heat, and it is probable that he used

these two agents as primary implements in his profession. In his writings is evidence that he knew of the stimulation produced by cold and the relaxing effect of heat. (9) Indeed, he went even further and directed that the cold be of short duration and preceded and followed by friction; this was followed by a quick recuperation of the body which then remained warm. One need only glance at any modern textbook on hydrotherapy to find the same methods used and to find the term "reaction" applied to the latter part of the above statement.

The Asclepiades used water in all its forms and had definite indications for the various methods of application. Some of the students who came from here followed their procedures concerning diet, exercise, and baths and became famous. Thus Celsus, who was the physician of Ovid and Fabius Maximus had what he termed the perfect therapeutic system which consisted of baths, friction and exercise. Antonius Musa cured the Emperor Augustus of his chronic catarrh and restored the poet Horace to health through the use of cold baths, and Charmis cured the maladies of the Philosopher, Seneca, through the medium of cold baths.

In Rome it is common knowledge that baths were the usual thing. Yet most of these were warm and used as a device for pleasure. Galen, the great physician of this era, used warm water and oils as therapeutic agents and seems to have been averse to the use of cold because of his experiments concerning the effects of snow and cold on the hands. (41) In the middle of the sixth century Aetius used cold water in

recent injuries and made some use of affusions in the treating of disease. Paulus Aeginata, in the next century used cold baths to treat sunstroke and anuria.

With the advent of the Dark Ages in Europe, the Arabs were the principal medical historians and in their writings are found enthusiastic accounts of the values of cold baths. Rhazes, at the beginning of the tenth century used ice water in the treatment of burns and the drinking of two to three pints of cold water in a half hour to decrease the temperature in fevers, smallpox, and measles. Avicenna used cold water by mouth for the relief of constipation.

From the Arabian era until the eighteenth century there is scant mention made of the use of cold in the treatment of disease, although undoubtedly it was one of the therapeutic methods in vogue, for Vander Heyden in the twelfth century collected three hundred and sixty cases of dysentery which were "cured" through the use of water, which method he considered as superior to the medical treatment used at that time. In the fifteenth century Michael Savonorola practiced a systematic use of the cold bath and had many disciples in Italy. Chief of these was Lanzoni who followed the Arabian practice of using ice water internally in fevers. In the sixteenth century Marianus Sanctus, also Blondus, recommended pure cold water as a "new" remedy which was rapid and certain, to be used in the treatment of wounds. Ambroise Pare, Fallopius, and Palatius used continued cold affusions to severe wounds

with good results. In the seventeenth century water was little used locally as there seemed to be a partiality shown to complicated ointments and pastes. However, for general application there must have been a continued use for in 1675 Barra of Lyons published a book on "The Use of Ice, Ice Snow, and of Cold" in which he mentions "cold water for continuous fever, and especially for erysipelas, pestilential fevers, contagious boils, frost bites, dysentery, the plague, inflammation of the throat, and lightness of the stomach." (41)

In 1667 Robert Boyle, more famed for other accomplishments, published a book which considered the properties of cold and environmental temperatures and their effects on the people. (23) Sir John Floyer published his "History of Cold Bathing" in 1697 in which he remarked on the value of cold and discussed the contemporaneous increase of disease as related to the lack of frequent or the absence of bathing.

In the eighteenth century we find the beginning of the scientific study of cold which is to culminate in the present day methods of therapy in respect to cold and its uses. In 1742 Chirac treated the Duke of Orleans' wounded hand with cold water and cured it and Chirac supposedly used this method as a routine measure. John Wesley in 1747, in his "Primitive Physich" gives twenty-four indications for the use of water. These include everything from fevers to rickets. At the same time Hahn was using cold water in smallpox and the other exanthems and Simon Fissot was using it to treat nervous diseases and bilious fever.

In the latter half of this century some of the most acute observations of the use of cold and its effects were made. Esmarch (41) claims it was German military surgeons who "re-introduced" the routine use of cold. In any event Smucker, in 1762, a general under Frederick the Great, used cold applications at the Battle of Schweidnitz and Huden, another general, used the same methods in dangerous injuries and inflammations. In 1785, both Percy and Lombard used cold as a general measure in surgical diseases. In America Dr. Benjamin Rush in 1794, at Philadelphia, used cold water in fevers, rheumatism, gout, yellow fever, and measles; it was Rush to whom Esmarch referred when he mentioned the best type of bladder to use in applying ice, for Rush invented and introduced the use of broken ice in a bladder. In New York Drs. Bard and Hosack used cold in fever therapy and in 1797 Peter Edes published a book on water and its medicinal uses.

In 1798 came the work which is often considered the actual beginning of cold as an active and scientific therapeutic agent. Dr. James Currie in Edinburgh worked extensively on the physiological and therapeutic effects of cold water and contributed his findings to the literature. In "Effects of Water, Cold and Warm, as a Remedy in Fever," Currie discussed the effects of sea water in sailors who had typhus fever. He noted that those who were forced to remain on the decks of the ships, by reason of the great numbers of those afflicted, and who were splashed with sea water seemed to fare better than the others who remained below deck. (51)

From his experiences with fever, Currie, in conjunction with Jackson, promulgated some rather extensive indications for the use of cold in fever: (1) To decrease cold in cold stages.

(2) To decrease heat in hot stages.

(3) To decrease spasm in the blood vessels.

(4) To support the powers of life till the diseased association dies away from the ceasing of their causes.

(5) To unload the bowels.

In addition to these principles Currie apparently noted "reactions" for he cautioned against the use of short cold applications in fever. This same man lowered the temperature of one Richard Sutton, a young and vigorous man, to 83F. by rectum, by the use of brine broth at 40° F. for forty-five minutes. (31) For the effects of the cold water on delirium, Currie tried it on a patient who was supposedly violently insane. This man was not influenced by emetics or tepid baths, and had been given as much as twenty-four grains of morphine in twenty-seven hours, all to no avail. On trying cold baths, the first one gave relief of symptoms for twenty-four hours, and five baths, subsequently, all at one time, cured the patient who afterward remained rational.

The nineteenth century brings forward those who were instrumental in the placing of crymotherapy as a method of treatment in the practice of medicine, those who spent their lives in the study of water and its effect on the organism. Priessnitz, the Silesian peasant, Winternitz who originated "Scientific

Hydrotherapy," and Simon Baruch, the father of the present day Bernard Baruch, who, in America, led in investigating and the formulating of therapeutic principles as regards hydrotherapy. Larrey, Napoleon's chief surgeon, reported in 1807 that at the Battle of Eylan he did almost painless amputations when the temperature was 19 ^{0} F. below zero, an approximation of modern day experimental work. It was Priessnitz who, by the curing of his own chest injury through the use of cool water, embarked on a life of hydrotherapy and did much to popularize the practice. His principles combined the theory of perspiration followed by cold application, which attracted people from all over the world, both patients and students. Wilhelm Winternitz put hydrotherapy on a physiological basis in accordance with the knowledge of the times and realized that "the most important truth of hydrotherapy, its primary action on the nervous system, was clearly brought out by Winternitz, who showed that even in fevers this effect is paramount and the antithermic effect is secondary." (^{9}) In 1826 was published a book by Beaupre who accompanied Napoleon into and out of Russia. In this book, from his studies, he divides the properties of cold into seven: (1) Refrigerating, (2) Exciting, (3) Sedative, (4) Astringent, (5) Tonic, (6) Debilitating, and (7) Perturbing. In 1849 and 1851 were written two books, which, if available, would be tremendously interesting as concerns the major considerations of this thesis. J. B. Arnott wrote "On the Treatment of Cancer b y Anaesthetic Temperatures," and J. H. Bennett's "On Cancer and

Cancroid Growths," are the books involved. (102) (104) Arnott is known to have used cold in bags and bladders for sedation to a part, but his book is unavailable. Guerrand and Richat in 1854, and especially Richardson in 1866 used refrigeration of tissues for surgical purposes extensively and established this method. However, they used ether sprays. Esmarch in 1861 contributed a survey of the use of cold and published his results. That he was enthusiastic is easily seen when he says "that according to my experience, I believe cold to be the most important and most powerful antiphlogistic remedy---." He maintained that in inflammation there is an increased temperature in the inflamed part, also a general increase in temperature from the increased textural changes, and from the increased flow of blood through the part. As to the rationale for use of cold water "Now if we possess a remedy which diminished the temperature of the inflamed part as well as that of the whole body, and which, at the same time, removes the sources of abnormal production of heat, I think we may call it, with full propriety, an antiphlogistic remedy, and that we really do possess a remedy in cold is amply proved by experiments, as well as by observation at the bedside of the sick." Esmarch further discusses the physiologic action of cold and points out that cold baths, affusions and cold bags would decrease the chemical activity of those reactions which cause or result in inflammation. There are nineteen case histories given in support of his contentions and these cases cover wounds, frac-

tures, rheumatism and eye injuries; ice bags were applied for periods of weeks and although pus, when present, seldom disappeared, an early dimmnition or cessation of pain with the discontinuance of morphine was usual. (41) How closely modern day clinical experiments parallel these results! Fleury was noted during this period for his ideas on chief methods of hydrotherapy. He considered douching as of primary importance. Brand used cold extensively, especially in the treatment of fever. The Brand Bath, a fifteen minute bath in which the water was first 70°-80° F. and then gradually decreased to 60° F., and friction applied was instituted when the temperature was elevated to 102° - 103° F. This method was of such success that it was Osler who said that "were the Brand Bath even more heroic, still he would use it, because it saves lives." (9) An interesting observation is recorded by Reincke in 1875. He reports on the rectal temperatures of three drunken men who had been exposed to cold. The first had a temperature of 27°C. ere he died, the second 26.4°C. ere he died, and the third, who recovered, 24°C. (75.2°F.) (58)

By the latter part of the nineteenth century cold as a therapeutic device was well recognized, but the understanding of its mode of action was not thoroughly understood. Simon Baruch did much to elucidate the values to be received from its use as well as to compile a textbook that ranked as standard in the field of hydrotherapy. Baruch's essential belief concerning the use of water in medicine was based on the theory

that while it had no specific antitoxic virtues, it aided nature against the manifestations of toxemia by improving the cardiac action, and vivifying the nervous system.

At the turn of the twentieth century there were many men who studied and wrote concerning the use of water, thus there are many standard texts on hydrotherapy. Kellog (68) in particular produced encyclopaedic works. In the last decade there has been a rather revolutionary change in the use of one of the forms of water, ice, in the practice of medicine. It may be said that Temple Fay and Lawrence Smith were pioneers in the reintroduction of the utilization of lowered body temperatures as a mode of hydrotherapy, while Frederic M. Allen has developed concepts of local application of cold in the form of ice to such an extent that they are receiving, at the present time, clinical experimentation to determine their efficacy. It is to these two latter considerations that further progress in the field of hydrotherapy most likely will occur, so it is the primary purpose of this thesis to investigate these fields and to properly situate them in the vast realm of crymotherapy or the therapeutic use of cold.

GENERAL HYPOTHERMY

Relationship of Crymotherapy to Hibernation

In recent studies of the effects of lowered body temperature in human beings, frequent reference is made to the word "hibernation" in a descriptive sense. This is used with refrigeration and freezing to describe most of the experimental work. Kovacs (71) and Talbott and Tillotson (102) take exception to the use of these terms as inadequate and incorrect and suggest that "hypothermy" be substituted. Freezing and refrigeration as terms to be applied are easily replaced. Freezing is contraindicated as a general word for no tissues which are frozen are even temporarily devitalized. Refrigeration is considered inapplicable for the word implies the object treated is refrigerated with the temperature reduced considerably lower than is compatible with life. Hibernation may or may not be a correct term and is less easily eliminated in favor of hypothermy.

As early as 1831 Marshall Hall was studying hibernation in hedgehogs. He noted that if they were immersed in cold water while hibernating, they could survive twenty-two minutes while ordinarily they survived only three minutes; he also noted the increased heart force in hibernation. Of recent years there has been much work on hibernation from which have evolved many theories. The word itself is best described as a "seasonal stupor seen in many invertebrates and vertebrates." (69) The invertebrates are of little import, other than phylogenetically

and the mammals are the primary vertebrates which we should consider. Mammals, of course, are normally homoiothermic, but it seems that those mammals, as the marmot, dormouse, hedgehog, raccoon, squirrels, chipmunks, gophers, and even bears, who do hibernate have a seasonal regression toward a more poikulothermic state. With this regression they have an ability to live in low environmental temperatures, and in food depravity. How this condition is accomplished or how it is maintained is difficult to explain. In the hedgehog, for example, whose normal body temperature is 33.5° to 35.5° C., when the environmental temperature is less than 14.5° C. definitely hibernates while his body temperature remains 1° C. more than the environment. This occurs down to 6° C. of environmental temperature; however, if the environmental temperature goes below 5.5° C., the body temperature is either maintained at 6° C. or the animal awakens. This shows that, in the hedgehog at least, there is not a failure of the heat regulating devices for if death if threatened there occurs awakening. (69) Thus environmental temperature would seem to be one of the factors that contribute to hibernating. The seasonal dimmition in the food supply is another important factor (36) and in hibernation there is evidently a decreased responsiveness, at least, of the temperature regulating mechanisms so that the organism can adjust to the unfavorable conditions of cold and decreased food by a periodic revertation to a more poikulothermic state. However, there are probably other factors as well that operate, for Cushing (36) found that if these factors were altered so as to produce hiber-

nation, but out of the regular season, there would be no hibernation. He believed that a "seasonal wave of pluriglandular activity" was responsible to a large extent for the phenomonen. Rasmussen (105) speaks of a hibernating gland in 1923, and contests Cushings claims of pituitary histological change. Rasmussen denies changes and states evidence should be obtained by examination before hibernation and after, although he contends there is naturally an increase in activity in the spring and in bleeding times. A "P" substance found in lymphoid tissue, closely allied with Vitamin D deficiency, has been mentioned as a causative agent in hibernation. There is found an increase in lymphoid tissue in the winter, in hedgehogs, and a decreased Vitamin D content; if dosages of Vitamin D are used in these hedgehogs, there will be no hibernation, and no lymphoid changes; on one hedgehog when Vitamin D was stopped, the animal then went into hibernation. Thus the uncertainty of the true cause and mechanism of hibernation is evident.

During hibernation it has been found that the respiratory quotient is decreased to an appreciable extent, This occurs quite regularly. Blood serum magnesium is increased and there has been found a decrease in sugar and adrenalin. These blood changes have been investigated and it has been found that injections of Calcium chloride will terminate hibernation and Magnesium chloride will precipitate it. Britton found that adrenalectomy had no effect in hibernation, but the animals died in the spring. Thyroid and epinephrine injections give hibernating animals trans-

ient effects of awakening. There has been found a decreased Basal Metabolic Rate and an increased force of the slow heart beat as well as a general tendency to increased resistance to toxic agents. The blood carbon dioxide and carbon dioxide combining powers are increased and all oxygen saturation remains unchanged. (69) There has been found evidences of dehydration in hibernating animals as well as a decreased gastric secretion. (105)

In human beings we find some of the evidences of hibernation when they are subjected to generalized reduction of temperatures. Man is not a hibernating animal normally, and while he is classified as "eurythermal" or able to stand wide variations of external temperatures, he is in contrast to those animals which are able to stand great variations in their internal temperatures. Thus when man is subjected to severely decreased temperatures over a sufficiently long period of time he cannot cope with it, his thermal regulatory apparatus fails, and lethargy, and finally death results. A constant finding in the recent experiments using general cooling has been a near constant respiratory quotient. (54) (69) (104) There has been no study of blood Magnesium, but blood chemistry has, in the great majority, been almost normal. (54) (69) (104) Buffon in 1749 demonstrated that cold alone does not produce a true hibernation, but usually a torpid condition that was physiologically different, and Marshall Hall in 1831 demonstrated it when he destroyed the brain and spinal marrow of a truly hibernating

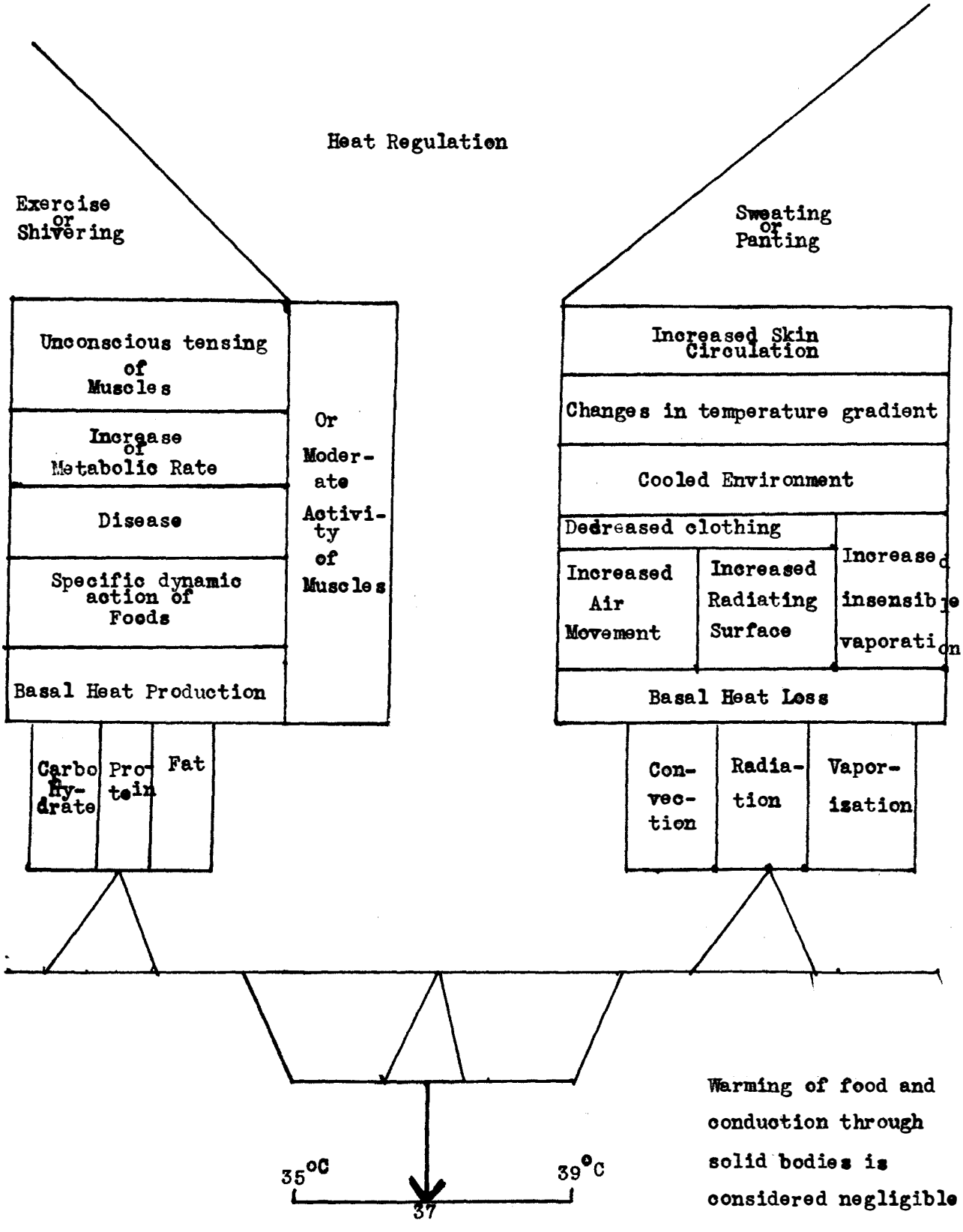
hedgehog and the heart continued to beat for ten to twelve hours. Cushing and Goetsch repeated the same thing. (36) Although there is some tendency to dehydrate in modern methods, there is usually found an increased gastric secretion to even the local application of cold. (19) Thus it appears that the new use of generalized cooling is approaching hibernation, and the ideal may be a "true hibernation," and while man retains his present mode of thermal regulation this ideal will not be realized. Hypothermy is a new word suggested by Kovacs (71), Talbott, and Tillotson (102) and seems more adequate in describing the conditions produced in cold therapy. Thus general hypothermy describes a moderate generalized reduction of temperature . Local hypothermy would be used for designating locally applied reductions, with medical applying to cold compresses or ice bags, and surgical hypothermy for the use of the various localized freezing techniques that are in current use.

TEMPERATURE REGULATIONS IN THE HUMAN BODY AND THE PHYSIOLOGICAL RESPONSE TO THERAPEUTIC APPLICATION OF COLD

Mechanism of Temperature Regulations

As man is one of the most precise of the homiotherms, it is necessary that he utilize a facile mechanism to maintain a body temperature that is compatible with life. The extremes of temperature to which man is environmentally subject are wide; his existence depends both on his ingenuity in fashioning extrinsic mechanisms to diminish the onslaught of these variations in temperature, and his inherent ability to alter his physiological mechanisms so as to successfully augment his extrinsic factors.

Mammals and birds possess efficient mechanisms that can maintain their normal temperatures in response to environmental changes from 0 °F. to 100 °F. To do this there is a balance between the heat lost from the organism and the heat produced. The heat produced in an animal body is the result of the chemical reactions occurring within that body and is thus spoken of as chemical regulation of body temperature while the heat lost from an animal body is the total of the physical forces in operation, so this phase is considered the physical regulation of body temperature. The constituents of these two regulatory devices normally balance one another. This is well illustrated by DuBois. (39)


Heat Regulation
Exercise or Shivering
Sweating or Panting
Unconscious tensing of Muscles
Increase of Metabolic Rate
Disease
Specific dynamic action of Foods
Basal Heat Production
Or Moderate Activity of Muscles
Carbo Hydrate
Protein
Fat
Increased Skin Circulation
Changes in temperature gradient
Cooled Environment
Decreased clothing
Increased Air Movement
Increased Radiating Surface
Increased insensible vaporation
Basal Heat Loss
Convection
Radiation
Vaporization
35°C
39°C
37
Warming of food and conduction through solid bodies is considered negligible

From the previous diagram it can be seen that heat production is essentially a function of chemical reactions. The exothermic oxidative and monoxidative process which are continually in muscles is an extremely potent force in heat production as shown by the rapid fall in temperature if an animal be curarized. (79) The chemical reactions found in the liver and other viscera as well as the action of the heart are continual sources of chemical energy and heat. The specific dynamic action of food is another potent force in chemical regulation. At high environmental temperatures this factor acts counter to those physical mechanisms which hasten heat loss; thus the use of a low protein diet in the summer as protein is that foodstuff possessing the greatest dynamic effect. Conversely, in cold atmospheric temperature, an increase in protein intake is beneficial for the specific dynamic effect acts to stimulate the body cells to a higher level of metabolism. The ordinary combustion of congested foods is a fluctuating source of heat and is considered the Basal heat producing factor. The changing basal metabolic rate is the measurable evidence of an increase of chemical activity in a body. The thyroid gland with its close association of the basal metabolic rate is of little influence in the immediate response of temperature regulation. Mills, (83) in young rabbits, found histological evidences of change decreased colloid content with an increased vacuole formation or a heightening of the epithelial cells or both together, in the thyroid gland when these animals were subjected to con-

tinued low temperature, but, no evidence is found of the immediate change in the gland, thus there is little basis for supposing the gland plays any great part in the more direct responses to changes of environmental temperatures. There is direct evidence that the adrenals, through the medium of adrenalin, actively participate in temperature regulation. This was demonstrated by Cannon in 1924 (28) and will be discussed under the body's response to cold. It is well known that a cold environment is the most potent influence to increased metabolism, thus it would be a great influence in the chemical forces of temperature control. Kellog (68) lists seven conditions which lead to increased heat production. These are: (1) Glandular activity, (2) Muscle activity, (3) Mental activity, a minimum effect, (4) Digestive activity, which supplies 30-40% of body heat with a temperature rise of more than .5 °F., (5) Brief cold water applications, (6) Low external temperatures, and (7) Prolonged high external temperatures.

Heat loss from the body is chiefly influenced by the body's response to a change in the external temperatures. The physical factors concerned in the loss of heat from the body are: (1) Radiation, convection, and conduction, with the last mentioned of comparitively minor importance; (2) Evaporation of water from the lungs and skin; these two factors account for about 90% of the heat loss of the body and are profoundly effected by the environmental temperature, the humidity and movement of the air, and the nature and amount of the clothing worn; (3) Raising the

ary means may play in such a manner as to produce almost any dissiminated physiologic or therapeutic effect." Thus it is the skin to which one must look for explanation of the greatest majority of heat loss.

Normal Physiologic Response of the Body to Cold

In studying the effect of cold on the body, there are logical reasons for selecting water as the mode of application. Water, which has been used as a medium for the transference of both heat and cold, is ideally constituted for the purpose. The specific heat of the human body is nine-tenths that of water, due probably to the high water content of the body. Air has only one-fifth. The ability of water to absorb and conduct heat and Best and Taylor state that water has a cooling effect fourteen times that of air, which two properties do much to determine the thermic effects of an agent. The facility with which water can be applied and the ease with which it can be changed from liquid to solid to gaseous are two additional characteristics which make it even more useful.

There are a multitudinous number of variables in considering the effects of cold on the human body, these concern temperature of the water, mode, length of time, and area exposed, amount of tissue exposed, and the reactivity of the patient as well as his general health. Cold, in itself, is a vital depressant as shown in such primitive cells and tissue, as the amoeba, white blood cell, and chick embryo, whose movement is suspended

when subjected to low temperatures, only to resume when rewarmed. But in the action of cold on the human body there occurs a reaction that accounts for the therapeutic effect. As Ewerhardt (43) states "Practically all the physiologic effects of the application of heat or cold are an expression of the endeavor of the heat regulatory mechanism of the body to maintain its constant temperature." This principle applies particularly to hydrotherapy but is of less use in the recent therapeutic applications of cold.

There is a difference in the physiological action of cold as it is used in hydrotherapy and the new methods of generalized hypothermy that are being currently studied. The temperature regulatory mechanism responds normally to a change in environmental constitutions in a way which is best suited to preserve body economy. To get a therapeutic response this mechanism is necessarily overcome for a short period of time, then the physiologic reaction enters and the regulatory forces reinstate the usual body conditions, and, as well, there occurs an overcompensation. In the newer methods as originated in America by Fay and Smith, this defeat of the thermal regulation is prolonged so as to produce an altered physiology throughout the whole organism.

In the application of cold to the human body there may occur three general reactions, a local, systemic, or a reflex action. The medium by which the response is iniated and consumated is

the nervous system. (101) By the effects of cold water on the skin, the nerve endings are stimulated both by the cold, on the cold spots, and the mechanical impact which also stimulates the receptor organs. There are definite centers affected by the impulses which are enumerated by Kellog (68) as (1) Sensory centers located in the brain, (2) Heat centers located in the spinal cord and brain, (3) Vasomotor centers located in the spinal cord, and (4) Secretory centers located in the spinal cord and sympathetic systems. These centers are classified functionally in the regulation of heat as thermogenic centers, thermogenic nerves, and thermogenic tissues. (68) There are three classes of the thermogenic centers: (1) Automatic centers in the spinal cord, which are in intimate contact with the thermogenic tissues and control heat production, (2) Accelerator centers in the brain which increase heat production by stimulating the automatic centers, and (3) Inhibitory centers in the brain, which restrain the action of the automatic centers. The automatic centers are considered as rather insensitive to stimuli which influence body temperature while the regulatory centers, accelerator and inhibitory are extremely sensitive.

The regulatory centers in the brain have been fairly well localized. Barbour (75) finds in confirmation of Ronson that heat regulation is confined primarily to two centers in the hypothalamus: (1) Between the optic chiasm and the anterior commissure, which prevents overheating and (2) a "more caudal center" for heat preservation; to destroy the center which prevents

chilling. Barbour states that a bilateral lesion "more candally placed" is necessary. Ostensibly Barbour is referring to that region of the hypothalmus which Bazett (10) finds just in front of the corpora mammilaria which seems to exert a controlling influence in heat regulation. As long as the hypothalamus remains intact, removal of cerebral cortex, thalamus, or corpus striatum does not destroy the controlling mechanism. MacLeod (78) states that there are apparently cortical regions that are important as regulatory devices in man for with certain cortical lesions there occurs either vasoconstriction or vasodilitation of the peripheral vessels.

The action of these thermogenic regulatory centers is transferred through the automatic centers via the sympathetic nervous system for the most part. Cannon (28) maintains that the effects of cold on the warm blooded animals are manifestations of both a sympathetic effect and the liberation of adrenalin. That adrenalin is important was illustrated in a series of experiments. Using denervated animals surviving and living normally, he subjected them to cold, thus results would be from either the cold or the injected adrenalin. As cold is known to decrease the pulse rate, if the rate was increased it would be in opposition to the effect of the cold. Using .0006 mgr. of adrenalin per kilo per minute intravenously there was found an increase of pulse rate of 34 per minute. In animals in a cold room there was an increase in the pulse rate of 12 to 43%, in an ice box

34 to 43%, sitting in lap and in a cold draught 43%, and with cold water in their stomachs, 27 to 64%. If the adrenals were rendered inactive by extirpation of one and denervation of the other, the above effects were not found, and shivering was much more pronounced. Cannon further found the sympathectomized cats have only shivering as an agent against cold, show no increase in B. M. Rate, and get a decrease of rectal temperature. When the adrenals are intact there is a decrease in the shivering but an increase in oxygen consumption, a manifestation of an increased metabolic rate. Cannon maintains that through this mechanism there can be the establishment of a heat liability of the body for one can use the weight, temperature, specific heat of the water and the animal. Thus in the animal a heat liability greater than 1000 Calories per Kilo gives shivering and increased heart rate of the denervated heart, greater than 900 Calories, shivering rarely occurs but heart rate is increased, and at 900 Calories, but with the adrenals inactive, the same animals may shiver for as long as seventeen minutes. The close relationship of the sympathetic nervous system with adrenal function is well established. In man, Cannon showed a 574 Calorie heat liability by giving 750 c.c. of water at 1 C°. This increased the B. M. R. 25% with the peak 15 to 20 minutes after giving the water; no shivering occurred with 750 c.c. of water at 34.5 C°., there was only an increase of 4% in the B. M. R. The thyroid supposedly also plays a part

in the response to cold as has been reported. (16) Serum taken from an animal exposed to cold will raise the B. M. R. of an animal into which it is injected. If the first animal has been thyroidectomized the second animal will not show a rise in the B. M. R. However, the conditions of these latter experiments are not shown and no definite results are noted.

The heat regulatory mechanism of the human body is effected reflexly from the skin and by the temperature of the blood flowing through it. (16) It is only the first of these two conditions which we are considering in this part of the paper. Kuntz (73) maintains that the autonomic system is a reflex system and the reflexes are influenced by somatic impulses, afferent in character, emanating from any part of the body, as well as from the higher autonomic centers in the brain stem and from the cerebral cortex. In the mechanism of heat regulation Pickering (89) states the response is at first reflex but that with prolonged application there is a stimulation of the heat center by the cooled blood. However, as the primary response is instantaneous, the total response, insofaras hydrotherapy is concerned, is reflex. Attesting to the strong cortical influences on the regulatory mechanism are these same investigators findings of a more marked vasoconstriction from physic influences than from the cold itself. (89)

The body response to cold is summarized by Kellog (68). Cold, through its action on the afferent fibers affects the accelerator centers which then influence the automatic centers to

perform in such a way as to cause an increased heat production through a response of the thermogenic tissues of which the muscles which store glycogen for heat and work, are the most important. The heart rate decreases which allows less blood to flow to the surface, the surface vessels contract, which lessens the area of blood exposed, perspiration is checked, which decreases evaporation, the erector pilae and other involuntary muscles of the skin contract which lessens the conduction of the skin, and respiratory movements are decreased which lessens the amount of air heated. It can be seen that the primary systemic effects of cold concern the integument. It has been mentioned previously that the skin dissipates approximately nine-tenths of the daily body heat loss so it is only logical to examine the effect of cold on the skin.

ACCEPTED PROCEDURES IN HYDROTHERAPY

Effect of Cold Water on the Skin

The uses of cold water in hydrotherapy are confined to the local reaction, reflex reactions, and the systemic effects. Most of the effects of cold water are manifested by the skin, yet, there are many reactions which concern the visceral action modifications. The varying effects produced depend on the intensity of the application, the temperature of the water, the area exposed, the time of exposure, and the state of the patient. There are many methods of varying the condition of application as baths, affusions, showers, douches, packs, and sheets. These all have there place in hydrotherapy and are used as principles indicate. The short cold bath is chosen as the example of cold water therapy for it illustrates a mechanism involved and as Riley believes "But without in any way discounting the value of other physical remedies, I believe that hydrotherapy, particularly in the form of short cold baths, will bring about more useful and desirable changes in the functions of the body than any other form of therapeutics." (90)

Before beginning on the effect of the cold bath, the word cold should be considered. There have been arbitrary water temperatures arranged according to sensation produced thus: 104° F. to tolerance is very hot, 98° to 104° F. is hot, warm is 92° to 98° F., tepid is from 80° to 92° F., cool is from 65° to 80° F., cold from 55° to 65° F., and very cold is from 32° to 55° F. (90)

Thus a cold bath by this definition would be water cooled to 55° to 65° F. The time relationship referring to "short" is defined as from one-half to three minutes. The beneficial effects of this type of bath are considered from a number of factors:

(a) The ability of the individual to react; a greater reaction gives a greater effect,

(b) Amount of surface exposed; greater the exposure, the greater the effect,

(c) The temperature of the water; less the temperature, the greater the intensity of impression,

(d) Mass or quantity of water applied at one moment,

(e) Length of time water is applied; only considered for three minutes here,

(f) Part of body to which water applied; the general rule is that area immediately beneath receives the greatest reflex response,

(g) The mechanical effects produced, which increase and intensify the effects of cold. (68)

It is to be realized that water is the carrier of the active agents, cold and mechanical impingement, and the effect on the organism depends on the variations found in the coldness and intensity. In the application of cold to the body there occurs a Primary Action and a Secondary Reaction. (90) (9) (72) (68) The final effect of cold depends on the mode of application and the temperature but mostly on the length of the application and the state of the patient. In the short cold bath the time limit is three minutes, the mode of application, and temperature of the water

inspired air to body temperature, accounting for about 2 to 3% of the heat loss; (4) The liberation of carbon dioxide from the blood in the lungs, accounting for 3 to 4% of the heat loss; and, (5) Loss of 1 to 2% in the urine and feces. (16)

To change the temperature of the body, either internally or externally there must occur an alteration in either the heat produced or the heat lost from the body. As this paper concerns the effects of cold, there are various alterations of the regulatory balance that result in a depression of temperature:

(1) Decreased heat production with decreased heat elimination,
(2) Decreased heat production with normal heat elimination,
(3) Decreased heat production with increased heat elimination,
(4) Normal heat production with increased heat elimination,
(5) Increased heat production with increased heat elimination,
(6) Increased heat production less than increased heat elimination.

Thus by considering these various possibilities there can be chosen a method that will best utilize the physiological mechanisms available. Of these available mechanisms MacLeod states "Under average conditions in man the main regulation of heat loss is effected by variations in the skin temperatures brought about by peripheral vasoconstriction and dilitation." (79)
From the above it can be seen that approximately 90% of the physical regulation of heat occurs through the skin . As Kellog (68) states "The skin, as has been aptly remarked, is a harp of a thousand strings, upon which one who is a master of necess-

is an all important part in the application of water. It is this effect which prompted Currie to state that its "not the cold that stimulates but the sensations which the cold produces." (68) This type of reaction can be easily seen in the web of a frog. A slight stimulation gives a brief vasoconstriction and then a slight dilitation of the capillaries; more severe cutaneous stimulation gives a quicker and more intense vasoconstriction and then a slight dilitation and showing of the blood stream; severe injury to the skin gives an immediate and pronounced dilitation and an almost complete stasis. This same type of reaction can be simulated in man, although it is only the first portion that is usually desired. (101)

The hyperemia that occurs in the secondary phase is conventionally designated as arising from nervous mechanisms. Ewerhardt (43) explains the hyperemia as being, in part, due to the continual supply of blood from the heart to the deep tissues, with the propelling force of the heart increaing the local blood pressure until it is greater than the resistance caused by the vasoconstriction and the blood finally rushes in with increased velocity and refills to more than the original volume. The exact mechanism of the dilitation of the capillaries he considers debatable. However, Huggins, Blocksom, and Wilson find dilitation when nerve supply to the region is denervated and report that as early as 1872 Roy and Brown noted secondary dilitation in the web of a frog when the sciatic nerve was cut. (62) Of course, in this second instance, there is no record of sympathetic nerves to the area. Bierman and Fried-

lander point out that the formation of a histamine like or "H" substance, which produce dilitation of the capillaries by direct action, and dilitation of the arterioles by reflex action are factors which are important in the production of the reaction. (78) Thus it seems logical that in the secondary response there is the combination of both nervous and local tissue change agencies in the production of the vasodilitation. To aid in the vasodilitation, friction and rubbing are commonly employed clinically for they have been found to aid the hyperemia. There are other procedures which enhance the effects of the short cold bath with respect to the reaction:

(a) Ere bathing,

1) Warm clothing
2) Warm room
3) Hot bath
4) Hot drinks
5) Hot Enema
6) Exercise, but not fatigue
7) Friction of skin till warm
8) Warm, dry skin
9) Good health and vigor

(b) In bath or in conjunction with bath,

1) Very low temperature
2) Short, sudden application
3) Pressure
4) Friction
5) Alternating hot and cold

(c) After bath,

1) Heat
2) Exercise
3) Friction

Effect of Cold on the Muscles

With short duration and with the aid of mechanical impression, cold increases the tone and elasticity, lessens fatigue, increases endurance, and tends to restore already fatigued muscles toward a more normal blood flow.

With prolonged application there is a decrease in muscle irritability and energy, the functional capacity ia decreased, and stiffness and clumsiness appear.

Effects of Cold on the Circulation

With the sudden shock of cold there is an instant long increase in circulatory rate and heart beat, then, there is a decrease. From the peripheral arteriolar constriction raising the effective resistanee, the blood pressure rises, the pulse is slowed, either from the cold or reflexly from the increased blood pressure, or from the lengthening of diastolic time. (11) With the peripheral arteriolar constriction Bazett finds there seems to be an associated dilitation of the large arterial trunks as evidenced by decreased pulse wave velocities. The heart has also been seen as enlarged by Hauffe in 1926 (12) from the effects of cold although his comments on the intrinsic reservoir of blood in the heart and aorta with its large branches and the pulmonic fields are not germane here. The tone of the heart muscle is probably enhanced so the peripheral vasoconstriction, by increasing the work of the heart and with the increased diastolic time, both exercises and rests the heart. With the dilitation of the periph-

eral arterioles and capillaries, there is a lessening of diastolic pressure and with the increased tone in the arteries there occurs an acceleration in the peripheral flow of blood. With continued cold there is decreased activity and rate of blood movement in the body. The continued contraction of the peripheral circulation throws an added burden on the heart, and the reflexed vasoconstriction which occurs in parts reflexly related to the area exposed further adds to the hearts' burden.

Effect of Cold on Respiration

In short applications cold increases both the rate and depth. The first reaction is a deep inhalation, then a momentary rest, and then a deep exhalation. If cold continues the respiration usually continues to remain deep and the rate is usually increased. Theoretically this could stimulate tissue activity from an increased oxygen absorption and carbon dioxide output. Dill and Forbes (33) found respiratory regulation effective in animals at 25°C. although they did note a trend toward acidosis as evidenced by a reduction of from one-fourth to one-half the alkaline reserve. However, they used prolonged severe cold.

Effects of Cold on the Nervous System

Local application of either cold or heat for short periods increase the sensibility, while long applications decrease it. The temperature of the water is extremely important here. The effects of cold water on the heat are well known, as the increased activity

created by short application, and the decreased activity from its prolonged use. The nervous system is intimately associated with all the effects produced and thus may be summarized by stating that short cold application stimulates activity, particularly sympathetic manifestations, and prolonged cold has the general effect of retarding activity as in other systems of the body.

Effects on Metabolism

The B. M. R. responds to short applications of cold by increasing the amount depending on the patient and the amount of stimulation. Prolonged cold may or may not decrease the metabolic rate depending on the heat regulatory mechanism's integrity.

Effects on the Blood

Riley (90) reports increased red and white cell counts as well as increased hemoglobin in short exposures to cold, and increased total counts in long exposed areas. Whether this is true state of the hemopoietic system or whether it is the result of the vascular changes is uncertain.

Effects of Cold on Digestive System.

The short cold bath produces an increased hydrochloric acid production as well as increased absorption in general and of phosphates in particular from the alimentary tract; in addition there is an increased peristalsis found in the stomach and intestines. (90)

The effects of heat and cold on gastric and intestinal motor activity has recently been studied by Bisgard and Nye. (19) Their method consisted of ingestion, irrigation, and by external application. By the insertion of balloons through the mouth and through ileostomy and colostomy wounds, and then transmitting the records onto a hymograph, a record could be obtained. They found that although the gastrointestinal tract was influenced by many extrinsic factors that cold to the abdomen would stimulate motor activity throughout the tracts, and would increase gastric acidity. If the cold water was ingested this same effect was reversed. Applications of cold th the thighs would engender the same motor response. Heat in general gave opposite effects than cold. Sano (92) found through denervation experiments which, when considered, led him to conclude that the motor response to ice depended on somatic stimuli to parasympathetic and sympathetic innervation of the stomach, but that the inhibitory effects resided in the ice contact of the ice or cold with the wall itself. The increase in free and total acid is so constant that Bisgard mentions it as a clinical test for achlorhydria. Stengel and Hopkins (100) noted a greater drop of temperature in the fundic portion of the stomach than in the pyloric which may be of some significance, although the difference was not great. Eberhard (40) corroborates Bisgard when he found that after ingestion of 250 c.c. of ice water or 90 grams of ice cream the motor end point of the stomach was advanced with a de-

lay in the emptying of from thirty to forty-five minutes. The influence of balloons of the type used by Bisgard and Nye on the initial tonus of the intestinal muscle may have been a factor in their results. (75) However, it would appear that it would be negligible. Whether the increased gastric acidity is from reflex action or from the liberation of histamine seems rather uncertain. (76) (19) Perhaps the surface chilling may increase the tone of the smooth muscle as it does in voluntary muscle, yet adrenalin is known to be released from cold, this should have an inhibitory influence on all but the sphincters of the alimentary tract. Perhaps it is a matter of degree, area exposed, and duration of the cold. Bisgard mentions future work to bedone on the sphincters.(19) Therapeutically, Bisgard's work indicates that while cold is contraindicated for appendicitis and peritonitis, it is of manifest importance for the relief and expelling of gas in distension, except in colicky pain wherein cold may further disrupt the integrated peristalsis. In bleeding ulcers, the ingestion of icy fluids would act to decrease gastric acidity, decrease motor response, and perhaps produce a beneficial vasoconstriction.

Effects on the Kidneys

With repeated baths, there occurs an increased function of the kidneys which include increased elimination of total solids and urea (90) although Kellog (68) finds a decrease in urea

elimination. Ewerhardt further states that cold effects diuresis by stimulating the micturition reflex and while the flow of urine is increased, if only temporarily, by the elevated blood pressure.

While it is understood that the above is only a minimal description of the effect on cold on the organism, it is sufficient to understand the rationale of therapeutic application. Through an understanding of the effects of cold which is not excessive on the body, it is hoped that a more logical investigation and a clearer interpretation of the more recent applications of cold in the form of ice and freezing can be gained. From a consideration of the effects of cold it is seen that certain conditions discourage the use of this agent:

(A) Conditions discouraging reaction, (68)

(1) Old age and Infancy

(2) Obesity or rheumatic diathesis

(3) Exhaustion

(4) Inactive skin or profuse perspiration.

(5) Very low temperature of skin

(6) Extreme aversion to cold

(B) Pathologic Conditions that Effect Reaction

(1) Nervous individuals give uncertainty of reaction

(2) Diseases of the peripheral vascular system

(3) Acute febrile infectious diseases may give toxic motor neuron changes

(4) Advanced Nephritis when there is a tendency to vascular spasm.

(5) Exophthalmic goiter

(6) Chronic alcoholics and morphine addicts which may have a vascular atony

(7) Cardiovascular disease with arteriosclerosis, and hypertension

There are many diseases in which cold as a hydrotherapeutic agent is used. Some of the uses in this field date with the beginnings of medicine, and some are of more recent use. The diseases in which cold is used are:

(A) The Sole Remedy;

(1) Sunstroke,

(2) Convulsions in children,

(B) An important adjunct;

(1) Typhoid
(2) Nephritis
(3) Myocardial degeneration
(4) Neurasthenia
(5) Constipation
(6) Moderate hypotension
(7) Functional stomach disorders
(8) Insanity

(C) A helpful aid;

(1) Pneumonia

(2) Local inflammation

(a) Rheumatism
(b) Mastoid disease
(c) Neuralgia
(d) Abdominal pain
(e) Peritonitis
(f) Ileus
(g) Scarlet fever
(h) Tuberculosis

(3) Chronic diseases in which all functions are depressed

(4) Asthenic and neurasthenic states

(5) Myxodema and states of decreased B. M. R.

(6) Diabetes and obesity if cautiously used

Of the use of baths in fever, Clendenning (31) has some definite indications; they are:

(1) A cardiovascular tonic which acts as a heart and blood pressure stimulant,

(2) A general sedative to the nervous system which induces sleep and allays apprehension,

(3) An eliminant by increasing the secretion of urine and the excretion of the nitrogenous waste products,

(4) A temperature reducer.

There are many methods of application of cold such as:

(1) Towel baths
(2) Ablution
(3) Sheet bath
(4) Drip sheet bath
(5) Wet pack, full or three-quarters
(6) Compresses, cold and stimulating
(7) Baths, general and local
(8) Douches
(9) Showers
(10) Baths containing chemical ingredients.

Besides the many uses to which a general form of cold water may be used as a therapeutic device, there are myriads of local applications that are used both by the general practicioner and the specialist. It is used with equal facility by the general man as an adjunct to mastoid "trouble," in which it "is so es-

sential a part of early treatment of mastoid disease that every physician owes it to his patient to use it," (31) and by the neurosurgeon as a postoperative adjunct. In general it may be said that local acute inflammation and congestion are indications for the use of cold, here the therapy is directed so as to produce vasoconstriction and relieve the pain. Likewise in trauma, wherein contusions and sprains are considered, and there is a likelihood of extravasation of blood and lymph, the vasoconstriction produced locally is beneficial in deterring the accumulation of extravascular material. However, it is not within the scope of this paper to review all the indications and uses to which cold as a local measure can be applied, it must suffice that general rules for the application be repeated, more with the idea of learning how cold normally acts and the present concept of indications for its use than with the idea of a comprehensive survey of the literature regarding its use.

So, with some knowledge of how cold water acts on the human body, and some knowledge of the accepted procedures in hydrotherapy, a more intelligent investigation of the new methods of applying frozen water or ice may be commenced.

THERAPEUTIC USES OF GENERAL COLD

In the last five years there has been a revival of a therapeutic agent that was at one time privately attempted. J. B. Arnott in 1849 published a book "On the Treatment of Cancer by Anaesthetic Temperatures" and in 1851, J. H. Bennett wrote "On Cancer and Cancroid Growths" which also regarded the use of cold as efficacious in neoplastic therapy. (47). These books, however, are not available for study. So, while Temple Fay is credited with a revival of cryotherapy in America, it must be admitted that predecessors are known and it is evident from the historical summary that reduced body temperatures had been experimented upon by men in the ninteenth century and observations concerning reduced body temperatures occured even prior to that time. In animals actual freezing of the tissues has been used. Fish, amphibians, and reptiles have been fully anaesthetized by immersion in cracked ice and water, then laid on ice slabs and operated with none of the effects of general anaesthesia. Pfeiffer in the use of new born rats shows that right after birth they do not maintain a high body temperature and if they are chilled in a refrigerator and operated on a bed of ice, they would usually suffer few untoward effects. (59)

The progression of reasoning and experiments leading to the first modern trial induced decreased body temperatures is interesting and illustrates a plan of scientific attack on a clinical observation with the evolvement of a new hypothesis.

In 1938 Dr. Temple Fay, a neurologist at Temple University, and G.C. Henry undertook a study to discover if spinal cord lesions or tumors would produce any temperature changes in the corresponding dermatomeres. To do this it was necessary to know the normal plan of segmental body temperatures. Benedict and Slack in 1911 ([15]) had studied skin temperatures, not with spinal cord stimulation, but from the standpoint of temperature gradients in different parts of the body. With the thermocouple as constructed by them, they found parallelism of temperature curves in response to heat and cold and as a general result. They postulated "Aside from the skin temperature, a rise or fall in rectal temperature of all other parts of the body." These men recorded differences in temperatures in various regions of the body and studied the effects of physical agents on the temperatures. In studying temperature gradients of the tissues. Mendelson in 1936 noted the difference of skin temperature in the upper exterminity thus he found the temperature of the skin on the back of the hand 29.24°C. on the forearm near the wrist, 32.02°C. near the elbow 32.44°C. upper arm near the shoulder 33.40°C. He further noted that in general temperatures were higher near the trunk and lower near joints. In 1937 Freeman and Lindner studied the surface temperature of forty patients on nine symmetrical points, took seven readings at each point, at thirty second intervals at a temperature of 24°C. and a 20% relative humidity. They concluded that the degree of bilateral symmetry is so close that one can use only one

side of the body for the measurement and analysis of data. There has been given only three examples from those who have studied surface temperatures of the body seeking sundry types of information. Fay, in his study, (44) used an improved type thermocouple and a galvanometer with which he could be accurate to within .2°C. (.36°F.) With these precise instruments he found that the average normal surface temperature was 3.5°C. (6.3°F.) lower than the mouth temperature. The areas of skin overlying the segments for the breast showed consistently higher temperatures than the rest of the trunk, which was fairly constant. The fifth thoracic segment was variable but usually was .5 to 3°F above the segments lying two inches to either side of it. (44) The head and neck areas were higher than the remaining body while the extremities were lower in temperature in all cases. The distal portion of the extreminities were found from 6.7°C. (12°F) to 11.1°C. (20°F) below the normal mouth temperature in certain instances, and from .1°C. (.18°F) to 4.6°C. (8.3°F.) in the male normal control groups in addition Fay found that irritation by heat and pain produced a hyporemia in segmental areas of stimulation and cold produced vasoconstruction and ischemia in the same reflex area.

The scarcity of either primary or metastatic neoplastic growths in the extreminities has long been known and often recorded. (45) Coley and Hieginbotham (32) in 1939 reported on 47 tumors of the extreminities in a series of 1,1211 primary bone tumors, less than half of these found in the

extreminities were malignant and only 2 metastatic. Mason (81) notes that carcinoma of the hands and feet comprise not more than 5 to 10% of all squamous cell epitheliomas . In contrast to these findings in the established frequency of malignancy in the breast region of females, in which segments, both in women and men, there is found a higher temperature than in the adjacent segments. With a depression of surface temperature that was recorded and noted by Fay and Smith, they decided to investigate the reason for this decreased incidence. The increased metastases to regions of increased vascularization and temperature such as the lings, brain, liver, and the central portions of the skeleton represent the same question for investigation with a single explanation hoped that would suffice to answer both queries.

In studying the effects of temperature on neoplastic tissues, the close resemblance of tumor tissues to embryonic tissue is accepted. Huggins and Blockson (63) studied the growth of red and yellow marrow in rats. They found that the red marrow normally regressed after the developmental period to yellow marrow in the distal portions which are the cooler areas. By transplantation experiments wherein these distal portions were put into the abdomen there occurred an increased red marrow perseverence. They observed that abdominal warmness was a factor in determining the marrow distribution after development. The elevation of temperature effects an increased hemopexis from the increased tissue metabolism, the secondary vasomotor effect or both, and

these conditions tend toward a persistence of red marrow. A decreased temperature by decreasing the disoassociation of oxyhemoglobin and changes in the carbonate bicarbonate ratio, and concentration and phi operates to remove the red marrow and replace it with the less viable yellow marrow. These investigations feel "Therefore that the temperature variations of the order present in the extremities of normal mammals and birds, significantly effect marrow activity." Huggins and Noonan in 1936 (64) found there was a great quantitive difference found in the reticulo-endothelial system content of the bone marrow of the central bones as compared with the more distant outlying centers, and, that changes comparible to those described in the previous experiments could be observed. The tissue constituting marrow is used as a good comparison for neoplastic growth because of the occurrence of prolific growth and mitosis. Thus, those experiments tend to illustrate that an increased temperature, is within physiologic limits, tends to increase cellular growth in the mammalian body and that decreased temperatures may be factors in regression of growth.

That a reduction of temperature does not kill cancer cells has been reported frequently. Gaylord in 1908 (52) found that the transplantable carcinomatous cells of the mouse were able to survive at a temperature of -- 195°C. of frozen liquid air, for at least 80 minutes and when thawed would regrow, although more slowly. Breedin and Farth in 1938 (24) reported on six different types of cancer cells

which could be preserved by freezing without their virulence being altered. They mention that Erlich kept cancer cells alive for 2 years at -- 8°C. An accompanying observation related that slow freezing of the cancer cells was less injurious to the cells than rapid freezing. Klinke in 1939 (70) recorded his experiments on embryonic and neoplastic growth after using liquid hydrogen and nitrogen as freezing agents. He found that round cell sarcoma of rabbits, after being subject to --253°C. as a result of exposure to liquid hydrogen, could reproduce as proved by vital staining techniques and the growing out and emigration from the explants. He found various resistancies to freezing in the different types of cells investigated. In freezing fragments of the embryonic heart of a fowl in liquid nitrogen for 5 minutes, on thawing he found evidence of fibroblastic growth and vital staining. Klinke concluded that the mammalian cells of malignant, embryonic of normal tissue can survive temperatures down to -- 253°C. So temperatures inimicable to cell growth do not depend on a severe reduction of temperature, but Smith has shown that temperature can be an important factor in cellular growth and differentiation.

In 1939 Smith reported (96) the results obtained from 700 studies made on the affects of temperature on the development of chich embryos. The optimal incubation of temperature in chick embryoies is approximately 100.5°F. Smith found that a "critical temperature" existed between 90 to 95°F.

in which there would occur a delay in development with a concomitant failure of cell growth, differentiation, and organization. He found that if embryos were subjected to a temperature of 90°F. for 48 hours, then allowed a normal temperature for development, they would show 100 percent malformation. Temperatures below 90°F. gave only delayed maturation. Thus Smith points out the similarity between embryonic and neoplastic tissue and considers the "critical Temperature" an important mechanism that may have therapeutic implications. Corresponding with the study of critical temperature in the chick embryo and the hypothesizing of the temperature factor in cellular growth , there is found another corollary in the physical spectrum, with its close relation to heat. In 1939 Smith and Fay presented a long paper (95) summarizing their data. This paper considers the effect of light as of importance, with temperatures, as a factor in the growth of cells from a broad biologic concept. Thus intense sunlight and sustained low temperatures gives a slow stunted maturity as found in vegetables above the timber line. Sunlight plus optimal temperature gives growth and maturity and darkness and increased temperatures gives an over-growth and delayed maturity as seen in plants in a dark cellar. (S.G.44. 38) thus generally speaking the physical spectrum plays some part in growth in cells. A suggested analogy in the human is the clinical history of the slow growing more mature forms of squamous carcinoma of the hands as opposed to the more rapidly active squamous carcinoma of

the cervix where the temperature is 1 to 3°F. above that of the mouth. The effects of X-ray for destruction of cellular growth while certain wave length of the ultra violet frequency are now being investigated.

LOCAL REFRIGERATION IN CANCEROUS CONDITIONS

With the establishments of certain critical temperatures for cell growth, plus the fact of decreased metastatic and primary tumors in regions of decreased temperatures, Temple Fay decided to try this theory of decreased temperature on human subjects. The first application was made in 1936 on a woman with a pelvis frozen from carcinoma. (44) (45). This patient had been taking .2 grain of morphine a day and was still suffering from pain, thus a willing subject for any alleviation of symptoms. Apparatus was fashioned of water at 36° F. in a closed system, and was delivered to the cervix. In hours, there occurred a relief from pain and the need for morphine was obviated. In three weeks there was evidence of fibrous repair of existing rectovaginal and vesicovaginal fistulae and definite microscopic evidence of degeneration of the tumor. After fives weeks of refrigeration this patient insisted on going home where she died 1½ months later from metastatic lesions. From the beneficial effects apparent on this first application grew the routine use of regional application of cold for severe cancerous conditions and the later investigation as to the feasibility of a generalized reduction of temperature when regional application is impossible.

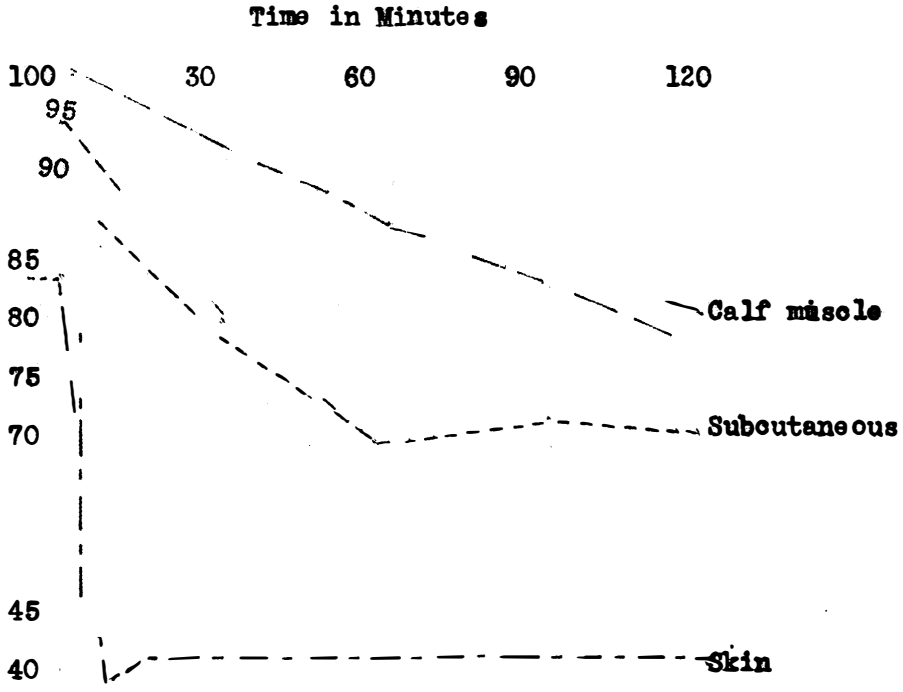
Smith in 1940 (98) reports the efficacious influence of local hypothermy or refrigeration in a wide variety of cases. There were found striking regressive changes in carcinoma of the uterus, breast, vulva, rectum, prostate, bladder, oral cavity, varying peripheral lymph mode lesions, thyroid, tumors of the brain, and even in some instances of bone tumors. In every case

in which direct application of temperatures of from 40 to 50 °F. were possible, necrosis and even actual disappearance of cells, as proven at autopsy from metastatic deaths, occurred. The method used is simple and evident but the mechanism is as yet obscure.

Interference with metabolism and cellular anoxia must exist, as well as a probable congelation of the cytoplasmic lipoproteins, when cold is applied. The process is different from actual freezing in which cells may be kept for long periods of time, for here the cells lose their viability in this critical temperature level. The unclear destruction and cytoplasmic degeneration which occur resemble the changes found with x-ray except that the x-ray destroys normal tissue including small blood vessels almost as regularly as tumor cells which often leaves a dense avascular cicatrix. With water at 40 °F for as long as five and one-half months, there has been found no damage to the skin or supportive tissue and the repair follows normal regeneration without scar formation.

To act on the tumor cells the decreased temperature must penetrate the tissues. This penetration is one of the prime objectives in the use of cold and Bierman and Friedlander in 1940 report (18) that cold on the surface of the skin and mucous membranes can cause appreciable diminution of temperatures in tissues lying beneath the surface. The extent of influence depending on the nature of the substance applied, its variation from thermal neutrality or the difference from the temperature of the body surface, the duration of application, and the region upon which it is placed. These men found, using thermocouples

1½ inches from the ice bag that water at 50 to 52 C. for 25 to 30 minutes on the cheek decreased the oral temperature 10 to 12 percent; water at 44° F. for 1½ hours in the rectum gave a 22 to 25° F. decrease in the posterior urethra; and in the leg the effect is best shown by a chart:



The fall of temperature is ascribed to the prompt vasoconstriction and the conductive abstraction of heat from the tissues, the insulating value of the subcutaneous fat manifesting itself in the appearance of the temperature gradient. Bierman concludes that "Conductive cooling profoundly effects the deep local, distant local, and systemic temperatures of the human body." That there is a decrease in temperature is important, but more important is the degree for the relationship of the internal temperature acquired to the critical temperature of the tumor cells

is the desired result. At present the critical temperature levels of human neoplasm is an uncertain thing and though good results have been obtained clinically no actual determinations of internal tissue temperatures have been included in the literature.

Sano and Smith (92) have recently reported a study on the effects of reduced temperatures on tumor cells in vitro. Using transplantable animal tumors as controls, they investigated the viability of tumor cells at 20 to 25 °C. (68 to 77 °F.) They first determined the time at 0 °C. necessary to half growth at 37 C., and found that in forty-eight hours all types studied grew, but at sixty hours only lymphosarcoma and mouse carcinoma, and these rarely. They then established which temperature would retard growth both after twenty-four hours at 37 °C., to let cells establish growth, and by putting cells immediately into a lowered temperature. The tumors studied were: (1) Reticulum cell sarcoma, rapidly growing in a 2½ year old boy, (2) Colloid carcinoma of the colon, (3) acute lymphatic leukemia, (4) Hodgkins Disease, and (5) Mammary Carcinoma of the Mouse, C 57 Lankeman strain. The results were compared to the controls used and although it was difficult to determine at what temperature all cells were destroyed because of individual differences and the fact that only one cell is needed to perpetuate a colony, certain rather definite observations were made. Sano and Smith noted "As a result these experiments have a critical temperature, around 22 to 24°C., which if maintained over sufficient periods of time results in a lethal interference with the neoplastic cells

in tissue culture." At 30°C, 86°F., there was found a marked regression in tumor tissue and at 22 to 24°C., 71.6° to 75.2°F., there was found a marked vulnerability of the tumor tissue. At the lower temperature nuclear changes were particularly effected, the mitotic changes perceptibly retarded. It is explained hypothetically by the changing in the physical properties from fluid to jelly like consistency during mitosis. For mitosis to be completed refluidification is necessary. With the fluid-gel balance in such delicate equilibrium, the decreased temperature supposedly can alter the condition. There is evidence that the total molar concentration of materials is less in germ cells and early embryonic tissues, and that neoplastic tissues resemble these embryonic and germ tissues. (92) Whether or not there is a correlation between this latter fact and Sano's idea on mitotic change has not been decided. There are important phases of cold checking or retarding mitosis for it is established that neoplastic tissues are more susceptible to x-ray during mitosis, and, thus, if cell division can be arrested, then irradiation should be more effective which would allow dosage to be decreased so it might then be possible to continue the effective period of therapy longer without injurying the normal tissue.

E. V. Cook (33) in 1939 reported that Asoasis eggs, after an exposure of 5000 r units found that cold at 5°C. got no recovery of the cleavage time as compared with his controls and the number of normal embryos increased as added time of exposure at 5°C. But this may be irradiated first and then found that cold might even aid the reparative processes, the cells recover

from the effects of x-ray more slowly under the influence of cold, but they recover ere proceed to develop so normal embryos, depending on length of time, are used. Temperature of 0 to 5 °C., (32 to 41 °F.) were found by Evans and Goodrich (42) during 1,300 r of x-ray, decreased the amount of injury to new born rats' tails' skins. These temperatures, however, are out of the critical level.

Crabtree and Cramer in 1933 (34) comment on the varying statesof susceptibility of cancer and normal cells to x-ray and state there is an increase in susceptibility just before mitosis. The respiratory system is the most labile of the known molecular systems in cells and it seems that irradiation effects this mechanism giving a progressive degeneration while anaerobic glycolysis remains relatively constant. This effect of radiation would be enhanced by cold if cold acted to depress cellular activity. These investigators did find that x-ray has a greater effect at lower temperatures. Mottram (84) corraborates the above findings by illustrating the effects of x-ray and reduced temperatures on broad beans as compared to the rats tails used by the parent investigators.

At Temple University there has been continued successful utilization of local hypothermy or refrigeration in the treatment of neoplastic growth. While no literature is yet available as to the effects of combined cold and x-ray or ultraviolet therapy, this phase is being investigated and experimental findings should soon be available. It is to be emphasized that relief of pain

and an improvement of general condition for periods of time that are variable are the only therapeutic claims that have thus far been established. There have been continual regressive changes found in size and morphology of the tumor masses treated, yet control of metastasis and disappearance of malignancy on biopsy have only occasionally been reported.

McCravey in 1940 ([80]) gives a summary of four hopeless cases of terminal carcinoma of the bladder. By sewing the mucosa of the bladder wall to the skin surface, thus marsupializing the patient, he effected a semipermanent suprapubic cystostomy. By use of special applicators he was able to apply cold at 40° F. The preliminary biopsies of all four cases showed Grade 3 carcinoma and pain was the major problem. In three of the four only local refrigeration was used. Three of the four showed negative biopsies while the cold was applied from 43 to 133 days. There were two fatalities from ascending infection and the two who lived had negative biopsies as well as relief from pain at the time of writing of the article. The major complication of the treatment seemed to be the chance of infection and consequent pyelonephrosis. Whether or not the biopsies showed the true condition present is problematical for there is a distinct possibility of extension beyond the bladder wall. In any event two of the cases were definitely benefited, all were improved temporarily, and two died whether because of the treatment or in spite of it, is unknown. The life expectancy was increased and possibly if preliminary surgery be done to decrease chances of renal infection

then the results may have been much better.

There is usually no dire tissue change found in the normal cells of the body in response to local cold. Smith ([98]) states "by and large, it may be said that only rarely are significant morphologic cell changes observed in normal tissue even when subjected to prolonged local refrigeration for as much as 5½ months."

To summarize briefly; It seems plausible that applying temperatures of from 40° to 50° F. to accessible tumors one may expect a relief of pain and improvement of general status of the patient, a regression in size of tumor mass, degenerative changes, necrosis, and perhaps even disappearance of the neoplastic cells.

LOCAL REFRIGERATION IN SURGERY.

Starting in 1929 and so before the work of Fay and Smith at Temple University, Frederick M. Allen was investigating the influence of decreased temperatures on the ligated limbs in animals with possible application to the field of human surgery. In 1939 Allen in discussing the physical factors in shock (7) mentions one of the standard procedures that was used in the production of secondary shock. This is the method whereby a ligature is placed around an extremity for varying lenghts of time, then with release of the ligature do the symptoms of shock appear, dependent in time on the length of ligature time, mass ligated, and, what is pertinent to this paper, the temperature of the pact. Allen had investigated the various factors that influenced the changes occurring in a ligated link and his observations have been complimented by those of other investigators. In defense of ligation as a justified procedure in producing secondary shock Allen then states that one can quantitatively control shock and standardize the degree of shock, exclude the nervous factors and the presence of dead tissues or blood clots, produce complete recovery of animals when desired, and possess a convenient method for studies to be made. Pain and nervous factors are mostly eliminated partly from the relative painlessness of the procedure and partly by the anaesthesia and nerve block produced by the ligature itself.

In the utilization of ligatures in an extremity to

produce secondary shock there are conditions similar to those found in certain surgical application of the tourniquet and thus Allen's studies which were dealing with shock were easily transformed into findings that were later developed into theories applicable to some phases of surgery, particularly of the limbs. The typical secondary shock following application and release of a tourniquet may range from trivial to fatal and is governed by the duration of the ligation and the mass and character of the tissue ligated. The length of time that the ligation occupies also governs the local effects of hyperemia and inflammation, and paralysis and anaesthesia. Gangrene arising from ligature application is considered due to lack of blood supply for a longer time than that which the tissues can withstand asphyxia and from the direct pressure effects in the zone of ligation, in the form of ulceration, necrosis, and thrombosis followed by gangrene of the more distant parts. (3)

In 1936 Wilson and Roome studied the effects of tourniquets on an extremity. (106) They found that after constricting the hind leg in dogs for seven to twenty hours, 69% of the dogs died on an average of 25 3/5 hours after release, as compared to 17% of the control. They found that with constriction of three hours, all their dogs recovered, three to six and a half hours all died. No mention is made of the environmental temperature or zone of ligature, but the site was presumably in the upper leg and the temperature that of the room. To prevent it was found that both amputation plus blood or plasma were

necessary.

Early in his studies Allen noted that the best type of tourniquet to be used was narrow and elastic. (2) As he says, "The flaw in the customary logic seems to lie in the fact that the degree of pressure required to stop blood flow is not greatly different whether distributed over a small or large area; but tissues are injured chiefly by direct pressure, therefore the greater extent of such pressure the greater the injury." The injury occuring from the tourniquet that are of importance depend on the species, the time, and, as is contended from experiments, the temperature. The local effects of ligature application which give ulceration and necrosis depend on the pressure applied over a variable length of time, 48 hours is usually the upper limit of time that gives no ulceration, after this pressure necrosis and ulceration usually occur, at room temperatures. The paralyses and contractures resulting from a tourniquet come either from pressure or as phyxia. Allen states (5) "On the other hand, in hundreds of experiments there has never been a single instance of permanent damage when the paralysis was produced by asphyxia alone, without any local trauma." Thus it is seen that the correct pressure, although easily adjusted to prevent arterial flow is an extremely important procedure in tourniquet application. Thus in the application of a tourniquet a narrow field is included to minimize the dangers of thrombosis. (6) The motor nerves are more susceptible to pressure and regenerate more slowly. (5)

The influence of decreased temperature is beneficial in allaying the pathologic changes as shown subsequently byBrooks and Duncan (25) who found that "If a rats' tail is maintained at a temperature between 0° and 3° C. the application of pressure for a period adequate to insure gangrene at room temperature, no gangrene occurs." Whether this fact is sufficient evidence is open to debate, the rats' tail is thin, gives a good line of demarcation, and presents signs of impending necrosis. These men later contend that temperature changes have not been proven to alter the development of gangrene, for there is no proof of altered metabolism, and, that the condition of the circulation was such that the receipts of nutritive materials and removal of waste products does not change with altered temperatures. The temperature range studied was 30 to 34° C. (86° F. to 93° 2 F.)

The asphyxia resulting from ligaturing a leg has been extensively studied. Allen has shown (2) that asphyxia of chicken wings takes nine hours of deprivation of blood, a rats' leg, twelve hours; and legs of rabbits, cats, and dogs, fifteen hours. He mentions these time intervals might have been longer had not ulceration from trauma and pressure supervened. These figures were taken at room temperature. Survival limits are specific as Allen says "It is probable that tissue metabolism is one of the important factors determining survival limit, and because of rapidity of metabolism the limit is likely to be shorter in the mouse, rat, and chicken than in dogs, and perhaps shorter in dogs than in man." Allen (4) found the survival limit in dogs intestine to be six hours or less, the liver with incomplete

investigation, one lobe for one-half hour, spleen three to four hours, pancreas, one-half hour, with death from fat necrosis, peripheral ganglion, number of hours." So not only is survival limit species different but is organ variable. The amount of tissue which has been deprived of nutrition is extremely important both in the production of the secondary shock following release and from the standpoint of rate of gangrene.

In animal experiments, Allen found that he could alter the usual clinical course of secondary shock with a local transudation of fluid on the application and release of a tourniquet by altering the temperature of the part. (3) In rats he demonstrated that ligature of a whole leg for twenty minutes at 45° C. gave death in two to three days; ligature below the knee for one hour and one and a half hours, gave necrosis with spontaneous amputation or death, at 38 to 39° C. for two to two and a half hours gave fatal shock, and low ligatures gave death in four hours. Thus prolonged ligature at close to room temperature showed serious results. He duplicated these experiments on other animals and got comparable results. Evidently the raised temperature by accelerating local metabolism and antolytic processes, created increased needs for a supply of oxygen and food, and for r moval of toxic waste products, and without circulation tissue death is hastened. When the same types of ligatures were used and the same types of animals, Allen found that the high ligatures that were fatal if used for thirty minutes would survive eight hours constriction if the limbs were placed in ice water; if two hind legs were placed in ice water, which would be fatal at room temperature, survive for five hours

ligations, stopping of the aortic circulation by abdominal circulation for one and a half hours, ordinarily gave death in one and a half hours, but if lower body were placed in ice water, survival was increased after three hours or more of constriction; in this latter case the rectal temperature would hit 27 or 28 °C. (80.6 to 82.4 °F.) but on rewarming the animals would be all right again. At room temperatures Allen found that the legs of rats, cats, rabbits, and dogs could be ligated for thirteen to fifteen hours or longer with a minimal danger." Elevation of only a few degrees of temperature multiply the asphyxia, so that either local gangrene or fatal shock may result within a fraction of the time required at room temperature." Using decreased temperatures, without freezing, Allen found that limbs could survive fifty hours or more.

To explain the effects of cold upon the tissue changes found there can be postulated a general metabolic retardation occuring in the part that is legated and exposed to cold. Goldschmidt and Light in 1925 (55) showed that in an arm exposed to cold water from 0 °C. to 18 °C. there was a decrease in the carbon dioxide saturation, and an increase in the oxygen saturation of blood taken from the antecubital vein. They explained this by a decreased metabolism of the tissue cells similar to that found in most chemical reactions subjected to cold and to that found in poikulothermic animals during hibernation. An additional factor is the cooling of the blood in the part which decreases the dissociation of oxyhemoglobin which decreased the amount of

oxygen available to the tissues for muscular oxidative processess. With decreased oxidation there is a decreased formation of carbon dioxide. This slowing of the metabolic processes is the sine qua non cold could not be effective. A slow flow should facilitate the call for oxygen by the tissues but if metabolism is so decreased that there is no demand then the oxygen is not required and thus the high oxygen figures obtained.

When the blood flow of a limb is curtailed and cold, in the form of ice is applied, there follows a appreciable drop in tissue metabolism. The presence of bacteria in the treated part demands attention insofar as the practical aspects of cold, in the form of ice, is concerned. The speculation arises as to whether the cold decreases the growth and activity of the bacteria. Zinser and Bayne--Jones say(109) "The resistance of bacteria to extremes of temperature depends on the species of the micro-organism contains endospores." It is generally known that bacteria resists cold more readily than heat and that actual destruction of organisms by cold is rare. Most pathogenic bacteria have a temperature of 37°C. as optimum for growth and reproduction, 15° to 25°C.(59° to 77°F.) as a minimum level, although staphlococci grow readily at 15°C. As salient point to be considered is the fact that one of the usual methods of preservation of bacteria is by means of freezing. Foster and Ralin (48) using Strep. glyceranaceus liquifaciens, fecalis, lactus, and acidopholus in experiments showed that the minimum temperature for metabolic

processes was usually 0 C, the minimum temperature for growth was higher. While these organisms differ from usual one found in the extremities, they serve to demonstrate biological trends. They explained the cessation of growth they found as a probable disturbance in the interlinking systems of enzymes commonly found in all cells. Four other possible explanations are also cited: (1) Accumulation of taxic products in the cell, (2) Changes in permeability or ion absorption, (3) Solidification of important lipids, (4) Too great a viscosity of protoplasm. These men further found that their largest bacteria crops were obtained at optimum or 10 C. below optimum growth temperatures. No important studies of tissue temperature have been made to find the actual reduction of tissue temperature under conditions of local freezing, but some studies, indicated elsewhere, show that the internal temperature does reduce, although the degree is not ascertained.

Allen in 1939 (6) reported a series of experiments concerning bacterial action under freezing. In a first series he injected rat feces into the legs of cats and dogs and could obtain controlled results as regards abscesses, necrosis, systemic malaise and intoxication. With short duration, 2 to 5 hours, of ligation and cold he found the effects slight and the infection worse, with a long period of tourniquet and refrigeration, 24 to 28 hours, the immediate benefit was greater than amputation, for the shock of amputation was absent, but at the release of the tourniquet, extensive gangrene,

thrombosis, and absorption of poison was so rapid that the animals often died in spite of early and high amputation. A second series of experiments using streptococci in rabbits yielded the same results. These experiments suggest that chilling may abolish the vital barriers to the difussion of bacterial products and that while the bacterial growth is inhibited, the toxin can spread with increasing freedom, from a chemical combination with protoplasm, and thus with release of constriction there is death despite heroic measures. (43) Bazett mentions that while cold decreases the growth of bacteria it also decreases phagocytic activity of the body and then when the body is rewarmed there is a resumption of normal growth. In other words, the effect of the cold is nonspecific, it not only decreases the growth rate of the bacteria, it concomitantly reduces the local metabolism of the tissue, decreases the circulation, decreases the capillary pressure, decreases lymph formation, decreases the body response to irritation, and even, as Allen has shown (2) decreases the efficacy of sera injected into the part subjected to cold. Allen had one clinical case of a fifty-six year old diabetic patient who had a leg infection; using ligation, refrigeration, and polyvalent serum he got a healing, but in two weeks a recurrence that required amputation which was done quite successfully with ligation and refrigeration. The practical lesson that Allen emphasized from his animal experiments is that prolonged ligation and refrigeration are contra-indicated in the presence of any

necrotizing infection if it is planned to restore the circulation afterward.

In general Allen's investigation showed that the dangers of constriction could be alleviated by the application of refrigeration. Wilson and Roome (106) enumerated the dangers of constriction as (1) interference with nutrition causing gangrene, and (2) circulatory depression following release. Allen demonstrated that tissues will withstand gangrene over longer periods of time than previously supposed, and if then the limb was to be sacrificed, with no release of ligature then refrigeration could keep a bloodless limb in good condition ere operation, pain and shock would be abolished, and perhaps the effects of trauma would be mitigated so as to allow more favorable healing. Thus from animal experimentation Allen arrived at a method for amputation that would obviate pain and shock, and eliminate the need for an anaesthesia.

SURGERY OF THE REFRIGERATED LIMBS

In May, 1941, F. M. Allen published the first of his papers on the use of Reduced Temperature in Surgery. (8) This particular article embodies a compilation of his findings and a method of application as used by him as well as indications for use. Due to the completeness of this thesis it will necessarily be rather closely followed so as a more perfect understanding can had. Allen states that with tissues deprived of all blood supply by tourniquet and the tissues influenced by decreased temperatures, there resulted much the same condition as meat preserved in the ice box. Using as high as fifty-four hours of refrigeration there has been no clotting of blood, no thrombosis found, the skin and other tissues remained fresh and intact and that paralysis or nerve injuries are minimized by cold.

1. Clinical Methods for Amputation

(a) The tourniquet should be two turns of rubber tubing, to give narrowest compression area, with a gauze pad beneath it, pure gum rubber 1 cm. in diameter has been found suitable. Reasonable care in the amount of pressure applied must be exercised although "clinical experience thus far has shown no signs of serious or lasting damage to the most arteriosclerotic diabetic vessels by constriction up to five hours at a temperature near freezing." The tourniquet is placed al low as possible to give a sterile field and yet allow sawing of bone and retraction. It is most important that the arterial supply be cut off from the limb. This can be determined by examining the

limb twenty to thirty minutes after chilling, if cyanosis is present in a limb that was elevated when tourniqueted instead of the usual blanching, then blood has been seeping through to tourniquet to the leg. The protection afforded the artery in the upper part of the calf makes this region undesirable as a tourniquet site, thus constriction is best placed either above the knee or below the tubercles and not between the two. The marks from the tourniquet vanish in one or two days after relief and in fifty-seven cases (7) no thrombosis were evident.

(b) Refrigeration was first accomplished by immersion in ice water but present use of ice bags, thin and flexible gum bags to which three to five teaspoonfuls of salt have been added, is considered better. If the limb is uninfected, after first surrounding zone of tourniquet with ice bags, limb is made vertical and the tourniquet applied in that position, then limb is lowered and put in ice bags to several inches above the tourniquet. In three to five minutes the skin is chilled so no pain, although sedation to alleviate apprehension may be needed, no anaesthetic drugs are required however, A temperature of 5 ^{o}C. (41 ^{o}F.) between the bag and the skin is the desired combination of adequate chilling and safety against freezing.

(c) Anaesthesia due to refrigeration is one of the most aspects of the new method. "Still more important is the realization that every form of anaesthesia known or used heretofore is limited to nerve anaesthesia,while refrigeration introduces the fundamentally new conception of anaesthesia of protoplasm." Thus tissue injury with subsequent shock is inhibited by cold,

thus the response, that according to Crile, came from duration and degree of tissue trauma, is largely obviated and surgeons may work for "the first time" in a shockless and bloodless field. The tissue injury remaining after operation is the only shock producing agent, this appears after the wound is closed and the temperature is increased to allow protoplasm to resume function. Thus shock is slight and thus a reasonably strong patient can return to the ward and eat a full meal for his constitutional condition is as though he had had no operation. To establish anaesthesia it requires from one hour in the emaciated skin to five hours in the rather thick thigh. In thin, weak, arteriosclerotics, two and a half hours for the thigh, two hours for disarticulation at knee or middle of leg, one and a half hours for lower one-half of leg or foot, and one hour for amputation of metatarsals or toes have been found to be adequate. (7) To test anaesthesia, if the sciatic nerve cannot be cut during the operation without attracting notice, or altering blood pressure or pulse, the preparation is considered as having been faulty. If the technique is properly managed the patient should not be able to know when the bone or nerves are cut.

(d) In the operative procedure, the ice bags are removed, the field is routinely sterilized and the operation proceeds as usual. No haste is necessary for the tissues stay cool, a moderate rise in temperature does not bother the anaesthesia although it is inimical to preservation of tissue and avoidance

of further shock. Iced saline and sponges should be used, a cool atmosphere is desirable, and if the operation is to be long, the limb should be kept in ice bags. When closure is imminent the tourniquet is released, and the bleeding vessels are tied, as the blood supply returns in proportion to the extent of the vascular tree present. The anaesthesia usually lasts long enough for convenient closure.

(e) The after care is guided by the state of the blood supply. If there is a reliable circulation present, the return to normal temperature may be al most immediate. However, if there exists a deficient supply of blood the temperature elevating must be gradual to insure the safety of the part. If there are signs of decreased vitality and mutilated tissues, the continued reduced temperature may inhibit shock production and maintain the metabolic status quo of the tissues until the collateral circulation is established to replace the deficient supply of nutrition, especially oxygen.

The problem of wound healing is considered aided by reduced temperatures. A fundamental surgical problem concerns the tendency of wound edges to agglutinate and seal in exudate which then may decompose and become infected. In the use of cold postoperatively there are mentioned some definite advantages. Ice bags will keep the wound open, allow free exudation and drainage. Theoretically and from observation the open wound will not become infected because of the retarding effect of reduced temperature on enzyme activity and bacteria. The profuseness of the

flow in these conditions shows that circulation and exudation are active and the bright red color of the blood is evidence of oxygenation and absence of putrefaction. Drainage tubes may be used in conjunction with the above for they do not irritate the cooled tissues. By gradually increasing the temperature, coaptation of the wound edges can be consumated within a few hours.

(f) In healing the tissue shows both the result and proof of the lowered metabolism. There occurs primary healing but at a much slower rate. Thus haste in returning limb to normal temperature is not to be condoned, particularly in arteriosclerotic limbs. Stitches are ordinarily removed in from ten to twenty days in this method, and this same retardation of postoperative treatment must be used in the whole postoperative regime. Primary union is favored by leaving tissue flaps which would ordinarily be considered as redundant, probably because of the shrinkage caused by the cold. The dressing should consist of one layer of petrolatum gauze and a few layers of dry gauze, then, one ice bag below and two above, not causing any pressure. The skin temperature is to be set at 15° C. a day, and by using additional layers of dry gauze a gradual raising of temperature commences, depending on the judgement of the operator.

(g) Bacterial infection and damaged vessel walls, or both, are the usual prerequisites for thrombus formation. The action of cold on the retardation of bacterial growth, on the lack of blood clotthing, and the lack of observed vessel wall damage lead to the belief that thrombi will not be formed. Clinical

investigation thus far has proved such to be the case. (6)

(h) After shock in amputations has been discussed somewhat elsewhere in this paper. It is known that, particularly in the thigh, tissue trauma usually produces varying lengths of debility. With cold this debility is decreased and when used in the lower leg the after shock approaches the vanishing point, which might make one think of earlier conservative amputation.

2. Use in Diabetic Gangrene

It was the inadequancy of methods of treatment of diabetic gangrene that led to the possibilities of utilization of freezing in the therapy directed at this condition. From Fay's observation (44) Allen knew that the temperature of extremities was normally lower than that of other parts of the body; thus the increased sensitivity to heat. In the gangrene associated with diabetes there may be either pure infection or pure arteriosclerosis as the etiology but usually there occurs a mixture of both. Heat raises the local metabolism which increases the need for blood. As arteriosclerosis tends to diminish the blood supply, the greater the sclerosis the nearer the approach to a ligated limb, heat, then, would have only a deleterious effect. By decreasing temperature, the needs of the tissue would more nearly approximate the available nutrition. This phenomenon occurred in some selected cases but in general Allen discovered that gangrene progressed in spite of the cold and the incurability of the sclerosis further negated the advisability of this particular method of treatment.

Freeman (51) in discussing the influence of temperature

on the development of gangrene, further emphasizes the relationship of blood flow to tissue metabolism and states "It is the blood flow in relation to the metabolic needs of the tissue that is significant." He mentions the easy possibility of gangrene through the use of heat and thinks "In general, it may be said that the temperature should be maintained at the highest level which does not increase the circulatory discrepancy as shown by cyanosis and pain." While he recommends the use of temperatures of 30°C. to 34°C., 86° to 93.2°F., as most benifitting in peripheral vascular disease, he mentions that when gangrene is threatening, that lower temperatures must be used. However, he does not state how low.

The use to which cold can be put in conservative surgery has already been mentioned while in fulminating infections there are also advantages that may be gained through the use of cold. The retention of a limb might mean death and the needed amputation would give sufficient shock for death to occur in these fulminating infections. In these cases refrigeration offers an alternative with the tourniquet adding the advantage of operation without the shock. Packing with ice would decrease the pain and advance of sepsis. The prompt application would permit amputation in a few hours without anaesthesia and with minimal shock. In case operations were inadvisable, the limb could be left for a few days or amputated in an area below ligature to decrease the area requiring packing, with the final amputation coming at some later date. The most important thing is a fulminating infection of the type discussed, is in the necessity

of never removing the tourniquet or letting it slip for then there is a rapid and fatal intoxication.

3. Amputations of Election

In low grade infections or dry gangrene the question of the best method of attack is often raised. Whether to do a low guillotine with subsequent high thigh operation or to do a major thigh amputation inially is the question raised. The age, general state of the patient, the local pathology, and the expected course are determining factors. High amputations are often resorted to because of the failure to heal of the low procedures. However, gangrene usually starts in the feet and the failure of tissue survival after a conservative operation seems likely to concern something connected with the operation. Operating injury must be divided into factors of local shock, infection, and edema; accessory causes are listed as: (1) too high a local temperature and (2) abuse of saline infusions giving increased edema. From the previous observations on the effects of refrigeration it can be seen that refrigeration combats all of these factors and will conduce healing after conservative surgery. Thus in those cases which do not demand a high thigh amputation it would seem to be the method of choice in reducing the surgical mortality by decreasing the number of major operations and making operations more easily tolerated.

4. Military Surgery

In the present state of world affairs military surgery is of prime importance and any apparent advantages which any therapeutic procedure seems to evidence should be thoroughly invest-

igated so as to realize the full potentialities. Allen discusses refrigeration with this in mind and urges further experimentation. The large number of military and industrial mishaps that produce mutilation of tissue and lead to the production of fatal shock offer a field in which refrigeration may be a valuable adjunct in therapy. The results of animal experimentation are used by Allen to demonstrate the possibilities of refrigeration: (1) Emergency facilities, nonmedical persons can carry out procedures using ice in warm weather and only preventing freezing in cold weather. Blalak and Mason in 1941 found that in twenty dogs they would get an increase in survival time when they were subjected to cold as compared with heat of a lesser degree than the cold. They contend that in the treatment of shock that excessive heat is more disastrous than excessive cold and suggest as a possible mechanism the vasodilitation of heat further depriving the vital centers of blood while cold, with peripheral constriction, forces the blood internally where it is more easily accessible to the vital centers. It must be noted that these applications, increasing temperature to 3.7 ^{o}C., or decreasing it 12.3 ^{o}C. by packing did not increase the animal's chance for survival but that the cold merely increased the survival time. (2) Tourniquets are often needed to stop hemorrhage and on release get varied degrees of shock. Efficient chilling would ward off this shock and allay the onset of gangrene when the tourniquet is applied over long periods of time. (3) Transportation could be made painless and with better preservation of the tissues than with large doses of sedatives. (4) Wounded would arrive at the

hospital ready for operation, and not needing any anaesthesia, (5) The effects of shock have already been described, but mere chilling especially in thick limbs is inadequate while if the tourniquet has been in place for eighteen hours precautions should be undertaken, even to amputation. (6) Infection can be held in abeyance with tissue vitality and resistance therefore preserved; if used for short periods one may get anaesthesia for operations without benefit and without apparent harm as regards the infectious process. But "Any extreme and prolongation of ligation of an actively infected part creates dangers of intoxication and death which necessitate precautionary amputation."

5. Embolism and Other Accidents

In the lodging of an embolus is found one of the most logical uses for chilling, the most important method of treatment in this condition. The usual procedure ere operation is followed and the postoperative temperature is minutely regulated, so as to let collateral circulation form. Bierman and Friedlander ([18]) mention the occurrence of two cases of embolism of the iliac arteries in which refrigeration was used. Both of these patients died but there was noted well preserved devitalized tissues after two weeks of refrigeration, with no spreading of gangrene, and an absence of the usual fetid odor.

In ordinary fractures chilling is of little value and it has been shown that an actual increase in temperature is more conducive to fracture healing. In open fractures, the procedure is governed as with other infected wounds and if there has been a ruptured blood vessel the procedure would follow that formulated

for an embolism. In fractures involving shock the tenets governing refrigeration and the prevention of shock are applicable.

There are certain obvious uses for chilling in plastic and reconstructive work but these await further investigation.

In the conclusion of this article (8) Allen urges the need for further investigation as to the benefits to be gained from a preservation of tissues through chilling. It must be ackowledged that although he has given many indications for the use of chilling, that this field is in an embryonic state as regards modern research and not until extensive investigation is completed will the wider benefits accrue.

In January of 1942 came the report (35) from the City Hospital in New York which considered the results of the technique and principles as had been enumerated in 1941. (8) It was found, in forty-five cases with fifty-seven major operations, that the outcome justified the method to a large extent. These fifty-seven cases were on unselected cases and poor average risks. Thirteen women and seven negroes were included in the forty-five patients. All but nine of the fifty-seven major operations survived. Of these, two deaths occured at two and nine months respectively when the stumps from the amputations were thoroughly healed. Of the remaining seven fatalities, four cases survived periods of two, four, five and six days, and in three cases, the survival time was two, three, and six weeks, respectively. These seven deaths were in general attributed to medical complications or septicemia, antedating the operative procedure only one death was admitted as being due to the operative procedure and it was

contended that this death would have been avoided in the light of later knowledge. Counting seven deaths in the six weeks period the mortality figures 15.5% in forty-five patients or 12.3% in fifty-seven operations. Considering the individual cases and causes of fatality this mortality rate is conservative. The group contends that every death had a rational explanation, that of an enfeebled patient who developed delayed shock and with the added strain of wound healing could not survive.

In fifty-seven amputations, this group at the City Hospital had twenty-one through the leg, with three deaths and five failures of healing, and thirty-six through the lower thigh, with four deaths and no failures of healing. It can be seen there were no operations through the upper thigh, the site of highest operative risk. The occurrance of death in the eight reamputations contrasts to the high or prolific mortality rate of reamputation and is evidence of the comparitive safety of at least trying a conservative amputation in a lower site to avoid both constitutional onslaught and the sacrifice of the knee joint.

The optimum level of amputation and the influence of refrigeration on this optimum is still undecided. However, with refrigeration there occurs a tendency for preference of the lower levels for there is then a lesser amount of shock and strain of wound healing in weak patients. Functional results from protheses below the knee are usually better when there is an intact knee joint. The ease of refrigerative technique below the knee and the greater effectiveness of postoperative chilling below the knee are two additional factors which influence to some extent

lower level choices. The question of operating through infected fields may have some less terror with the use of refrigeration, particularly in the lower leg. These investigators have operated through fields of known infection and then either closed the wound tightly or left it open, and, although they do have occasional mild, or brief febrile attacks, the lower procedure seems to have advantage over the dangers of the higher operation. Whether chilling decreases local vitality and weakens physiological barriers so that diffusion of bacteria or their products into the general circulation is facilitated or creates dangers of thrombosis or embolism is not definitely decided. The possibilities have been discussed elsewhere in this paper.

The gist of Allen's beliefs are admirably summed in a final quotation. "The remarkably good preservation of general strength, the practical absence of postoperative pain or need for sedatives, the retention of appetite and spirits, the limitation of necrosis or infection even under unfavorable conditions, and the total absence of thrombosis or embolism all testify to the lack of injury from either the reduced temperature, or the tourniquet and establish the life saving value of the new method in the surgical treatment of peripheral vascular disease." (35)

Although the results of other clinical investigations have as yet not entered medical literature to any great extent, McElvenny (77) reports an interesting isolated case in August, 1941. A fifty year old man, and a poor risk patient, had one leg off at the knee and the other just above the knee by a train,

the wounds contained a considerable quantity of mud and dirt. On entrance his blood pressure was 30/0. He was given acasia, tourniquets were applied to both legs and the stumps wrapped in sulfanilamide. In eight hours his blood pressure was 50/10, in ten hours he was irrational, had a sinus tachycardia and a severe pain in the chest. In twenty hours there emanated a very foul odor from both stumps and a diagnosis of pneumonia was also made. He received neoprontosil and his temperature stayed at 101.4 in the axilla. At this time ice without a tourniquet was applied to two inches above the proposed site of amputation. In one hour, there was no pain in the stumps, soon there was no odor perceptible, and a little later the man was rational so that mouth temperatures could be taken. With continuous application of ice the temperature of ice the temperature reduced to 97.2° F., so he was blanketed and then the temperature went to 101° F. In fifty-eight hours from admittance the blood pressure was 110/60, temperature was 101° F., and the progress of the pneumonia was halted. Thus under ethylene anaesthesia the stumps were elevated, tourniqueted, and amputated through the thighs. No redness, enduration, or ecchymosis was noticeable at the site of amputation. There were no postoperative complications. In five days the patient was smoking and in six weeks the stumps were healed. The amputated parts showed no evidence of gross infection or inflammation, there was no odor, the muscle appeared red and healthy, fascia and blood appeared fresh. There were no microscopic examinations reported. McElvenny was uncertain whether the drugs or the ice was the determining factor,but acknowledges that the ice

did stop the pain, aided in combating shock, and stopped all odors from the stumps. There was a marked improvement in the patient after the use of ice. The skin fragments not included in the ice were all gangrenous. Thus the author says if refrigeration "Physiologically and bacteriologically the procedure would seem to be sound," and urges that Allen's claims should be examined clinically as they might find wide application in civilian and military life in which doomed limbs might be saved and infection in hopelessly traumatized limbs may be held in abeyance until hospital facilities are provided.

GENERALIZED REDUCTION OF BODY TEMPERATURE

Following the successful use of local refrigeration for relief of pain in accessible carcinomatous lesions and because of the degenerative changes seen in these lesions, Temple Fay decided to try the effects of generalized lowering of body temperatures on the deep seated and inaccessible cancerous growths. In October of 1938, a case of ulcerating breast carcinoma was treated with local application and the primary site was almost cleared, as well as the glands on the neck. This particular patient had metastases to the vertebral column and brain already so it was decided that it was a suitable case for the initial endeavor of general hypothermia. The objective was to establish a general body temperature similar to that found in the extremities in order to study the effects on metastatic growths. In this initial case there were little effects noted on the carcinoma but there did occur a temporary cessation of pain which Fay and Smith thought merited further investigation. Since that time various studies have been made and gradually this method of therapy is being properly allocated to a suitable position in the field of therapeutics.

Selection of Cases for Generalized Reduction of Body Temperature

Since this method started as a hazardous procedure, and is still in rather an experimental stage, only hopeless cases in extremely poor physical condition were treated. These cases had all the surgical and radiological therapy that was possible and

inary anaesthesia and then packed the patient with cracked ice. This patient also received amytol. In twelve hours the breathing and pulse rate was imperceptible so from fear of cerebral anoxia, she was brought out of the ice and her rectal temperature adjusted at 90° F. It was considered that the heavy sedation had caused the untoward effects and this has been remedied in subsequent investigations. In instances in which avertin and amytal was used, there were two deaths recorded as being due to cerebral edema so barbitals were considered as unsafe.

The next method of anaesthesia used was evipal, which allayed the shivering. Finally the best anaesthetic agent was found to be Cyclural, a Methylcyclohexenylbarbituric acid. This is used intravenously in 5 to 15 gr. amounts. In more than eighty inductions there have been excellent results with this drug. (46) The group at the Lennox Hill Hospital in New York have a more elaborate form of preparation. Chloral hydrate or bromides are given the night before induction. Luminal is given the next morning, then a tube is placed in the stomach for later sedation, and avertin or evipal intravenously or rectally is given immediately preceding the induction. Fay contends (45) that if heavy sedation is omitted there will be no cessation of respiration, no cerebral edema, and no absence of pulse or kidney function.

Following the preliminary anaesthesia to allay shivering the patient is moved to a room at 58° F., or from 50-60° F., with a relative humidity of not exceeding 20%. The stripped body is placed on a rubber sheet, a loin cloth is applied, and the trunk and upper thighs are packed with cracked ice, "no larger than nut coal."

common in four of nine examined. Newman and Berris report (85) that sinus bradycardia and an alternation of the Q.R.S. were frequent with a generally prolonged R.R., Q.R.S., and R.T. found. No cases of auricular fibrillation was found in fourteen cases. Also "no cardiac damage occurred as evidenced by normal curves following treatment," gives evidence of the cardiac effects in apparently healthy persons. Fay reports (45) death from cerebral edema and cardiac failure in 15% of cases in a small series of cases and believes they occurred from an added burden on an already defective heart in restoring peripheral circulation. Smith, Fay's coworker, in the report of one hundred cases, (97) says that of five cases severe myocardial degeneration, three had existing coronary disease and two had none. Thus a defective heart is generally considered in all investigations to be a poor risk. In studies on younger individuals with strong hearts no mention of cardiac involvment is made, (102) although there was one cardiovascular death in an older patient in their series.

2. Hematology

Smith and Fay (97) find a tendency for the hemoglobin to drop although the red blood count rarely fell more than 1,000,000 during the entire period. The white blood count usually increased on an average of from 10 to 15 thousand with a prompt return to normal when treatment ended, which suggests a peripheral vascular influence. Reich at Lenox Hill (54) reached the same conclusions after the first day of treatment. Although in the first day he found a slight increase in hemoglobin and the red blood count. In one patient, a leukemic, he found no change in the white blood

count, and in an acute myeloblastic leukemia which had two twelve hour treatments, the white blood count dropped 40,000 after each period of treatment, no change in the 95% myeloblasts present, only to return to original figure; thus he corroborates Sano (92). Reich also found the sedimentation rate and platelet counts were decreased, while cell volume increased. Newman and Berris ([85]) report one change in blood type during treatment.

3. Blood Chemistry

Smith and Fay (97) find that when fluid balance is maintained there was no evidence of nitrogen retention, there may be some drop in urea, and the chlorides and sugar were not effected. Newman and Berris (85) in five patients found an increase in N.P.N., and urea nitrogen during and after treatment, creatinine rose during and fell to normal after treatment, sugar was uneffected and the carbon dioxide content was not significant. They do not think effects were from dehydration, but do not mention individual patients. Beruhard (54) mentions the difficulty of accurate observations in the eleven patients studied at intervals of twenty-four, forty-eight, and sixty-four hours. He found (1) No changes in N.P.N. (2) Plasma protein showed no significant changes, (3) Chlorides in normal limits, (4) Serum Calcium, Phosphorus, and free chlolesterol constant, (5) Red cell volume increased 14 to 20% in four instances, (6) Initial sedimentation rate increased in all eleven, but back to normal in forty-eight hours of cold. The negligible effects as emphasized by Smith and Eberhard would seem to outweigh those of Newman from the standpoint of a greater number of cases studied.

4. Basal Metabolic Rate

All investigators who report on the B. M. R. agree that there was some decrease, although in short exposures there occurred an increased rate. Unsatisfactory reports from technical difficulties were so frequent that not a great deal of validity can be attributed to any of the investigations. Geiger at Lenox Hill maintains that there is a definite decrease in twenty-four hours, a greater effect being noticed at forty-eight and seventy-two hours respectively.

5. Renal Function

With the regulation of anaesthesia and the prevention of dehydration the kidneys were able to function. There were no pathologic urinalysis found when the above conditions were fulfilled, although Mueller, (85) found casts, albumin, acetone and in increased N.P.N. with dehydration. The urinary output was found by Newman to equal the intake, with the specific gravity depending on the intake.

6. Respiratory system

It is through the respiratory rate that the general condition of the patient is well judged. In general there is a correlation in the pulse and respiratory rate. Most often there remains a normal rate, 20 to 26, throughout the treatment or there may occur some slight depression, with rates of 5 to 10 rare in frequency and generally indicative of some unnatural process. Fast respiratory rates are equally indicative of complicating pathology. If there are numerous metastatic growths present in the lungs, or if there are present other

Recently there has been developed by Dr. L. Phillips of the Nash-Kelvinator Company a cooling unit using circulating Prestone; Richards at the Toronto General Hospital has a cooling cabinet, (85) and the Thermo-O-Rite Company of Buffalo, New York, has manufactured a blanket for continuous refrigeration. (102) An intranasal stomach tube is inserted and a rectal resistance thermometer is introduced. Vaseline gauze is placed over the eyes to prevent corneal damage from the cessation of tearing occasioned by the reduced temperature. The refrigeration is continued until the rectal temperature reaches 88° to 90° F., then the ice or mechanical device used is removed, the bed remade with clean dry linen, and the patient left exposed to a room temperature of 50° to 60° F. Shivering usually occurs as the body temperature descends from 97° F. to 91° F., and 95° F. is the temperature most frequently occurring. This shivering can be allayed by preliminary sedation, but, as has been mentioned, the sedation implies a more hazardous mode of behavior than shivering. The length of time necessary to reach the desired rectal temperature varies. Fay and McCravey (46) assert that one or two hours is sufficient, at the Lennox Hill Hospital, one and a half to two and a half hours is the usual time necessary although in one stout female twenty hours were needed, and Newman and Berris need four to eight hours to get the desired rectal temperature. There appears to be a difference both in the type of patient and the mode of application, however, as the rectal temperature can be closely watched, the time factor is not as important as it would at first seem to be. After the de-

sired body temperature is obtained, the maintainance is effected by means of ice bags or blankets depending on the desired result.

For the alleviation of restlessness during the period of hypothermia paraldehyde by nasal tube is more generally used, from two to eight ounces in a 20% solution in acasia whenever there is indication of its use. (46) This can also be given rectally in five or six ounce doses. At Lenox Hill they found paraldehyde too irritating when given by stomach tube, thus they use sodium amytal or sodium luminal for the alleviation of restlessness, and, as well, lavage the stomach with one quart of normal saline, a pint at a time, once a day. From six to thirty-six hours may elapse between sedations as the patient tends to sleep unless he is aroused. (46) Although no food or fluid was given in early experiments it was later considered necessary to supply something to combat dehydration. Thus, now physiological saline in 10% dextrose is the accepted fluid given through an intranasal tube. Two ounces every two hours is used by Fay (45) while the group at Lenox Hill use two ounces every hour. Fay mentions that small amounts of whiskey may be added, and further states that if patients are aroused and encouraged, that soft foods could be given although due to dimunition of the swallowing reflex, they may choke. No food is given although the period of treatment may last from five to eight days. The length of time that elapses from induction varies with the condition of the patient, the type of pathology present, and, apparently, with the experience of those in charge. Fay and Smith (45) have kept patients for five to six days at temperatures around

80 to 85 F. with no subsequent abnormal effects. Their longest recorded elapsed time is eight days with a temperature between 88 and 90 F. The usual periods of time are from nine to seventy-two hours depending on the state of the patient. Temperatures of 78 F. have been reached at the Lenox Hill Hospital. A patient was left at 79.2 F. for two hours with no subsequent abnormality. (54) Talbott and Tillotson kept the temperature of a thirty-nine year old woman under 80 F. for six hours, two hours of the six were with a temperature under 75 F. with a low reaching of 74.6 F. This woman survived with no abnormal effects. (102)

A slow return to normal temperature is desired at the termination of the treatment, from six to ten hours being desirable. The return is aided by warm blankets, hot water bottles, warm coffee enemas, and warm food. A moderate dose of paraldehyde is easily interpolated at the right temperature range. This eases the discomfort of restoration of circulation to the periphery. On emergencies it is not uncommon for the temperature to go to 101 or 101.5 F., for one or two days. A sluggishness of sensorium is usually noted for from twenty-four to forty-eight hours, and relief from pretreatment pain may not be determined for the first twenty-four hours.

There are certain conditions which necessitate a termination of the treatment: (54) (1) An irregular respiratory rate or one above thirty-six per minute, (2) A pulse over 120, although fibrillation has been treated with quinidine while under treatment just as well as at normal temperatures, (3) Pulse irregularities, and, (4) Stupor. It was with the purpose of

studying the effects on cancer and its metastatic lesions that general temperature reduction was undertaken. The prime observation made was the relief from intractable pain that occurred with cessation of treatment. As study and new observations have shown, this form of therapy revealed that it may have further possibilities. Through a study of the effects on the various systems of the body, an understanding of the mechanism may be gained, and, possibilities for further use may be investigated.

Effect of Generalized Reduction of Body Temperature on the Systems of the Body

1. Cardiovascular system.

The pulse rate, on induction, shows a preliminary increase, and then there uniformly occurs a decrease, not in proportion to the temperature, however. There may be an absence of peripheral pulse with an apex beat of 60 to 100. Usually the beat is regular and it is unusual if the temperature is lower than 85 for the pulse to go below 50. (54) Newman and Berris find the usual pulse around 30 unless there occurs a sinus arrhythmia or auricular fibrillation.

The blood pressure usually follows the same general curve. Induction may give either an increase in both systolic and diastolic or a decrease in the first and an increase in the second. In long exposure the blood pressure decreases and may be imperceptible. Fay and McCravey (45) state that with less sedation with drugs both pulse and blood pressure can be obtained.

Newman and Berris (85) found that blood pressures could be obtained in only 30% of the cases, with a systolic below 80 and a diastolic rarely obtained. In one hundred cases of generalized reduction Smith (98) found four cases in which there was a steady decrease in blood pressure until death. Three of these had metastatic lesions in the adrenals.

There is a profound constriction of the peripheral vascular tree during treatment, with no evidence yet found of Raynauds Phenomenon. Fay and McCravey (46) say that no cyanosis should be present at levels or 80 ^{o}F. rectally, or above, and that in eighty inductions the body color remained good. Both Smith ([97]) and Newman suggest the circulatory rate is nearly doubled in the periphery, and at Lenox Hill they find the circulation time is slowed.

With a decrease in pulse, decreased blood pressure, general vasoconstriction, and a decreased circulation time, it would seem that the cardiac output would be doubled. Kassman (54) reports there is always present some abnormality in the T wave in the E.K.G., in four instances below a temperature of 84 ^{o}F. the T wave was characterized by a summit immediately after the Q.R.S., a return to the baseline, and a final summit smaller than the first, while Kassman says "it is surmised that it may be the first evidence obtained in man in support of the dipolar nature of the regression process in cardiac muscle." With no alteration of blood concentration of calcium or phosphorus, he suggests that some pathologic process is responsible rather than the simple effects of the cold. He found auricular fibrillation

chronic conditions of the pulmonic age, there is an increased susceptibility. Dixon (54) in twenty-six patients with fifty-six periods had five Bronchopneumonias of which four had pulmonary metastases. In eighteen patients whose lungs were clear only one got pneumonia, as the result of aspiration of vomitus and mucous. Occasional cases of bronchopneumonia have been reported by other observers, usually with the direct evidence of pulmonary metastasis.

7. Digestive System

No food is given while treatment progresses; saline in dextrose into the stomach constituting the sole nourishment. Daily evacuations have been noted by Newman in one case. (85) Fay mentions the lack of evacuation (45) That some absorption must take place is evidenced by the action of drugs and the urinary findings. Two postoperative fatalities are noted; (1) From a mesenteric thrombosis and (2) from an acute hemorrhagic pancreatitis in a morphine addict. Smith mentions three fatalities from pancreatitis in morphine addicts. (97) Morphinism supposedly has some type of deleterious effect on the pancreas, which may have predisposed it to injury.

8. Nervous Stystem

In the nervous system is found themechanism for the associated responses of generalized reduction of body temperature, although the exact mode is undetermined. Fay and Smith studied the neurological responses in forty-two patients in eighty-three periods of reduction. Hamilton in 1937 observed the effects of

of hypothermic states in animals. He found there occurred a progressive descending paralysis of the central nervous system. The higher nerve centers of locomotion, voluntary movement, attitudes, equilibriation, learning and site are first lost. Then, swallowing, biting, corneal and flexor reflexes, and finally the medulary centers with respiratory failure and death. The responses last to disappear were the first to return. (57) In the study of Fay and Smith (47) there were similar results found in man. Cerebration was progressively delayed, with mental faculties fairly well preserved until 93° F., retrograde amnesia was usually present while body remained below 92° F. Dysarthria began at 93° F. with practically a cessation of response at 80° F. They discovered that appreciation of pain, heat, and cold was not lost during or after the treatment. The deep reflexes were increased from 97° to 85 F., but with no change in the abdominal reflex. The period of hyperreflexia corresponds to shivering stage, but as the temperature approached 78° F. there occurred the abolition of deep tendon, abdominal, and gag reflexes. The pupils remained equal, regular, and normal in size, but the response to light became progressively more sluggish and was abolished at 78° F. Newman and Berris (85) in temperatures from 85° to 88° F. found that the patients did not remain unconscious, but slept from twelve to fifteen hours a day. They could talk, and although their speech was slow and thick, their thoughts appeared orderly. Difficulty in swallowing, regular micturation in both sixes, and amnesia of events following recovery were constant findings by these men.

In 1941 Talbott and Tillotson (102) reported on the effects

Although Smith admits(98) that only impressions can be given,he found changes in tumor tissue when temperatures of 75 to 90 F were maintained and 96 to 120 hours had elapsed,and,often 300 hours were needed. Then he found the same type of regression as in local refrigeration: (1) Difference in staining,(2) hydropic and granular changes in the cytoplasm,and,(3) karryorrhetic and karyolytic changes in the nucleus,though there was a lack of intensity of response that was seen with local refrigeration. However Paltauf (54) found no regression of primary tumor or metases and could not demonstrate any unusual cell alterations or changes that showed the effects of the lowered temperature. Smith (98) found that in the majority of cases the size of the tumor mass was decreased with at least a temporary clinical improvement; Although no actual destruction of metastatic tumor tissue was claimed,the author believes the method does lenthen the life expectancy of an individual. As a general observation at Lennox Hill,there was found no visible or palpable decrease in size or any softening in the carcinomatous growths.However,in the 24cases studied,they found results in two cases which contradicted general findings. A nodule the size of a walnut in a cancerous thyroid,with a tracectomy present,disappeared a week after treatment. In a carcinoma of the transverse colon with metastases to the liver which was stony hard and palpable 4 fingers bdlowthe costal margin,after a second induction there occured a softening and recession of the liverso that it was barely palpable and a relief from pain for 12 weeks after which time the pain recurred in the chest which was filled with metastatic lesions. This

pain could not be relieved. Smith reports (98) remarkable relief ofosymptoms in a woman with choked discs,cerebral metastases,and severe pain. Leukemias have shown transitory effects of decreased cell counts in response to therapy but no claims of permanent benefits have been made.

The dangers of generalized hypothermia are well recognized and seem to be correlated in a general way to an already weakened system. Cardiovascular deaths and cerebral edema deaths usually follow in patients who have had previously damaged hearts. Pneumonias are found as a cause of death almost exclusively in those with previously damaged lungs,either from metastases or other pulmonic disease. Vaughn (104) considers the procedure too hazardous for even hopeless cases of carcinoma although in 6 cases of generalized carcinomatosis he had 2 living at 7 and 8 months respectively,with freedom from pain for 3 months and neither using narcotics at the time of writing. Pancreatitis was found in a small percentage of deaths in morphine addicts,which agains lends lends circumstance to the hypothesis of systemic strain on diseased systems. Nephritic deaths are not reported although in the blood studies of one patient which Vaughn (104) discusses as dying from cerebral edema the pretreatment levels were N.P.N. 82,Creatinine 6.1,Urea and Urea nitrogen 58; after treatment these levels were 24,0,and 10 respectively,but the time after treatment when these were taken is not mentioned.This was a case of Grade 3 Carcinoma of the Cervix with a generalized carcinomatosis of 6 months duration.

The use of general hypothermia in morphine addicts is

condoned despite the occassional mortality. There is found a metnod whereby the addict is spared the withdrawal symptoms to a large extent. The cessation of addiction has occurred for variable periods of time and in some (85) there was a prompt resumption of the habit. The use of the type of therapy is necessarily an adjunct in support of the total therapy directed at the patient. In schizophrenia Talbott and Tillotson (102) in a study of 10 cases,are enthuiastic over the prospects of a new approach to this problem. In patients under 40 years of age and in the early stage of the disease,definite improvement was noted. They state that the results obtained warrant further investigation into its application in schizophrenia and that various phases and types of the affective mental disorders or the manic depressive psychoses could be investigated along similar lines.

Hypersensitiveness to Cold

In any therapeutic use of cold there is present the possibility that there might occur a reaction on the part ofthe patient to the cold. While this has never been reported in conjunction with any of the recent applications of any type of hypothermia,it is a factor the investigator must recognize. There has been a total of 83 cases reported in medical literature (27). 22 of these patients have been studied at the Mayo Clinic in the last 10 years,the age incidence ranging from 15 to 59 years. In 1865 Bourdon mentions the first record of urticaria due to cold from localized cold to a part and in 1872 Blachez discussed urticaria following the swallowing of iced food.

The relation of the modern cold pressor test of Hines and Brown (60) in which the reaction is based on the principle of a hypersenstive sympathetiv nervous system to the cold is somewhat correlated to the response as seen in those who exhibit a generalized hypersensitiveness to cold. There are three general theories in the production of this reaction((1) Allergic immunopathology,(2) Humeral,or,(3) Neurovascular. Brown and Barker (27) state that there is no single mechanism constantly present but that a different one prevails in each instance. It seems conceivable that combinations of the three theories may also be responsible in some of the cases.

In the 83 cases of hypersensitiveness reported in the literature,29 had systemiw reactions,and of these,18 developed syncope. 15 of those with syncope were swimming at the time of onset and 4 of these had to be rescued. In the 22 cases studied at the Mayo Clinic (60) 14 had systemic reactions,11 of these with syncope,9 after swimming,and 4 had to be rescued. It seems that the study at Mayo's would be more exact than those of the previous century so more authority should be given them. All of the cases reported by Brown and Barker had local symptoms on exposure to wind,cold water,or to a cold environment,thus in hypothermiv therapy a provacative test is available.Adsen and Allen have such a test (43) that consits of immersion of the hands in cold water at 60°F for 5 minutes and then observing the local reaction. Both local and general symptoms can be produced by the injection of histamine. These reactions are indistinguishable from the cold response,both to the patient and the observer.

Ewerhardt (43) states there are twosatisfactory methods for desensitivation: (1) Immersion of the hands in cold water for 1 or 2 minutes 3 times a day for 3 or 4 weeks,or,(2) the subcutaneous injection of .1mgr. or less of histamine twice a day for 3 weeks. The first of these methods,if they are equally efficacious,would appear to be the more practical. Histamine or a histamine like substance is supposed,y the etiological agent in the production of both local and systemic reactions although it has never been found present. Nevertheless, resistancy to cold has been produced through its use. Thus, through the use of tests for hypersensitiveness and the treatment suggested,if such a condition is found,can hypothermic therapu still be used in those sensitive to cold.

COMMENT

In this paper there has been an attempt made to study the mechanism of cold, and its action on the human body in the practice of medicine. Investigation first engendered a study of the body's reaction to a moderate reduction of temperature, exemplified in the response to cold baths. It was found that the commonly believed stimulative effect of cold can be substantiated by scientific observation. Then, with a further reduction of temperature a new field was encountered. It has only been in the last ten years that these new possibilities have been examined. The work of Frederich Allen in New York and Temple Fay and Lawrence Smith at Philadelphia pioneered scientific research in respect to these recent innovations in this new use of cold.

The therapeutic advantages of localized reduction of temperature promise a more extensive utilization of this principle, particularly in surgery of the extremities and for the reliefe of intractable pain which is so commonly associated with terminal carcinomatous states. In surgery, the use of reduced temperatures offers ostensible, although as yet not fully investigated, advantages, especially in traumatized and infected tissues and in those conditions in which amputations is indicated. Cancerous lesions which are accessible have been found to be profoundly effected by the applications of cold, with regression of cellular characteristics and an unexplained relief from pain as the common results.

Generalized reduction of body temperature does not seem to offer the same possibilities as a mode of treatment because of its difficulty of administration and the relative lack of encouraging

results while a decreased body temperature relieves intractable pain and is thus applicable to suffering in inaccessible carcinoma, the effects in most cases are transitory. However, it may be stated the repeated periods of general hypothermy have been used with good results. That the potentialities of Fay's work have not yet been realized is attested by the encouraging reports of work done in schizophrenia and drug addiction, so, that perhaps at a later date this method of therapy will assume established position in the field of therapeutics.

It should be noted that both general and localized hypothermia are still experimental and while evidence is being gathered slowly as to their efficacy it will be only with further research that the can assume their position in the relief of pathological conditions of the human body.

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