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HYPOTHERMIA

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* This series of papers is the result of a conference on *Hypothermia* held and supported by The New York Academy of Sciences on November 13 and 14, 1958.

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INTRODUCTORY REMARKS

Albert S. Gordon

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Extensive use has been made of modalities such as temperature and pressure to alter the rates of reactions within cells, tissues, or the organism as a whole. Information gained from these approaches has amplified considerably our knowledge of the basic nature of biological processes.

In recent years, special attention has been applied to the influence of lowered temperatures upon a variety of cellular activities. This interest has stemmed primarily from two sets of observations: the ability of hypothermia to preserve, for almost indefinite periods of time, the life of cells, particularly those of reproductive origin, and the finding that hypothermia can be employed as a valuable adjunct in cardiac and neurosurgical problems.

These provocative findings indicated that the time was ripe for a broad comprehensive consideration, at both a physiological and a biochemical level, of the properties of the hypothermic state. At the suggestion of Emil Blair, The New York Academy of Sciences has undertaken the sponsorship of this monograph. Included are many important facts regarding the basic character of the hypothermic state and the effects of lowered temperatures on circulatory, respiratory, hepatic, renal, endocrine, and nervous functions. The last part of this publication deals with factors relating to cooling and rewarming phenomena.

INTRODUCTION: ZONES AND STAGES OF HYPOTHERMIA

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Hypothermia refers to body temperatures lower than the usual ones. In mammals and birds, the so-called warm-blooded animals, the core of the body is ordinarily at 35° C. or higher. Only when regulation of body temperature is interfered with or overpowered does the core temperature fall. While some species are known to dispense with customary regulation, as when entering a state of natural hibernation, most mammals require forced cooling in order to become hypothermic.

Artificial cooling can be inflicted quickly either by external means, as by contact with cold water, ice, or other such refrigerant; or by internal cooling,

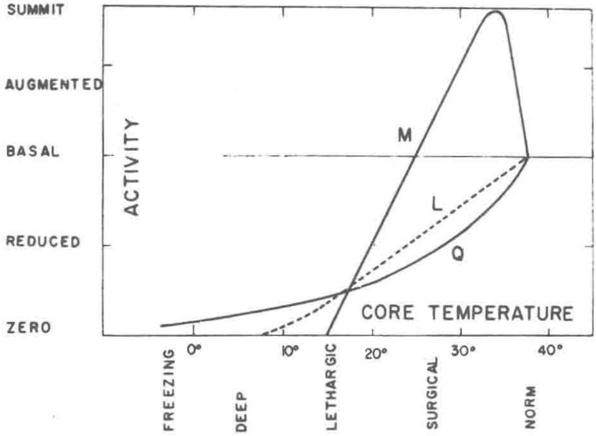

FIGURE 1. Activity ratio in relation to body temperature. Stages of activity (*ordinate*) are represented as above or below the basal that occurs in euthermia or norm. Zones of core temperature are given names (*abscissa*). Sample activities M, L, and Q are each shown in relation to hypothermia.

as by the extracorporeal circulation of blood through cooling coils. The former method is adequate in small animals; the latter is commonly resorted to in animals weighing more than five kilograms. Compensatory warming is often prevented by anesthesia or narcosis. Later, rewarming is aided by surface warming or by warming the coils containing the externally circulating blood. Sometimes localized warming, as of the heart region, is used.

The task of students of hypothermia consists of measuring the changes in function that occur with body temperature. These functions, here referred to as activities, all eventually diminish in rate or intensity as temperatures decrease. However, temporarily some functions such as oxygen consumption or heat production markedly increase. Each activity may be related conveniently to the temperature of the tissue manifesting it (FIGURE 1).

Activities do not change in parallel. Hence physiological distortions result at all low body temperatures, relative to the integrated state at the usual temperatures. Upon further cooling, some activities cease; these cessations are referred to as biological zeros. Zeros occur at different temperatures for various activities; zeros help to characterize the functions.

Having designated the various stages of activity as basal, augmented, summit, reduced, and zero, we can usefully distinguish zones of body temperature at which the modifications occur (FIGURE 1). We can think of the usual body temperature as a norm, and successive zones of hypothermia as

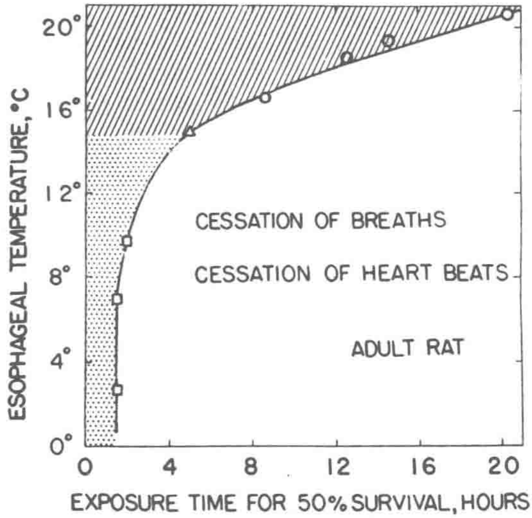

FIGURE 2. Exposure times (*abscissa*) that were survived by 50 per cent of unanesthetized rats at various body temperatures (*ordinate*). Below 15° C. artificial breathing was administered during the exposure, and was required for recovery. Darkened areas are the viable zones for exposure.

surgical, lethargic, suspended, and freezing. As we shall see, none of the zones is necessarily lethal.

When activities have ceased at their characteristic temperatures, they usually recover upon rewarming. After a sufficient time, however, their cessation becomes irreversible. Death is characterized by the irreversibility of some essential function; but it may also be characterized by the failure of some complex or coordination. Each activity may recover within a limit of time; only when low temperatures prevail for too long a period does death result. A temperature-time contour thus defines the limits of viability (FIGURE 2). These time limits are found, however, not only near 0° C., but also at temperatures of 15° C. to 25° C. where there is no known suspension of a measurable activity.

Methods of study of hypothermic states include not only observations on intact animals and all their parts, but measurements upon separate organs and tissues *in situ*. Cold blocks and narcoses thus become tools for the study of numerous functions. Isolated tissues can be observed for continuance of activity and for survival. Various models and chemical systems may be set up for comparison with intact tissues.

Indeed, the complete hypothermist can learn valuable lessons from many phenomena in cells and tissues; energetics, mechanics, enzymes, equilibrium states, kinetics, phase shifts, electrolyte effects, electric potentials, and optical activity. He will delve into processes of movement, conduction, transmission, cell division, adaptation, regulation, protein synthesis, and growth, as well as blood flow, breathing, and other usual organ activities. Also he naturally will learn these lessons from a wide variety of organisms.

Evidently a great number of activities need to be followed at low temperature. Temperature is a dimension in the physiological constitution of a tissue, and the tissue's response reveals certain of its capacities. We have the further task of seeing how each modified activity fits a place in a total pattern of the cold organism. That pattern describes, more or less adequately, the organism that will not tolerate hypothermia indefinitely.

In my estimation, what physiologists of hypothermia need most is, first, a good theory, more comprehensive than the pioneer one of Arrhenius, as to how the concept of heat as a form of molecular energy applies in living systems; and, second, a valid theory of what kills organisms that attain various low temperatures. For mammals, we have three prominent notions about cold death: (1) destruction of some limiting process or structure, (2) stoppage of energy transformations at low temperature, and (3) disproportion among retarded processes. Each of these notions has guided a host of investigations; we now find available large bodies of detached information that have not yet crystallized our understanding of how hypothermia limits life.

VIABILITY OF SUPERCOOLED AND FROZEN MAMMALS

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On March 23, 1756 a Swedish peasant intoxicated with brandy was bowled over by the wind and fell asleep in the snow. He was found next morning frozen stiff, and was put into a coffin ready for burial. Later in the day a physician arrived unexpectedly and examined the body. The face and extremities were ice-cold, the joints immovable, the eyes fixed open, and there were no signs of breathing or heartbeat. However, the physician, S. Naucler, thought that there was some warmth at the pit of the stomach and ordered the arms and legs to be rubbed while he applied hot fomentations to the trunk. As a result, the patient gradually revived and, next day, was recovering. This case was reported fully in the proceedings of the Swedish Academy of Sciences (Naucler, 1757) and in *The Scots Magazine* of 1759.

Many similar cases have been described during the past 200 years. The best documented of these is Laufman's account of a Negro woman in Chicago who lay in a drunken stupor at an air temperature between $-18°$ and $-24°$ C. all night. When she was rescued the next day she was pulseless, but the heart was beating 12 to 20 times per minute and she was breathing 3 to 5 times per minute. The rectal temperature was 18° C. and, judging by the subsequent rate of rise, probably had never been below 16° C. The extremities were much colder and became so severely frostbitten that it was necessary to amputate the legs below the knees, and all the fingers and one thumb were lost. Nevertheless, she survived (Laufmann, 1951). The question is whether a high blood alcohol level favors survival from severe hypothermia, or whether the intoxicated merely are more liable to expose themselves. Thus far there is no evidence that any human being whose internal temperature has reached freezing point has recovered.

More than a century ago Bernard (1876) found that the internal body temperature of mammals could be reduced by immobilizing them in contact with chilled mercury or snow. Guinea pigs so treated recovered after the deep body temperature had reached 18° or 20° C., but at 16° C. breathing and heartbeats stopped and were not resumed when the animals were rewarmed. In 1881 Horvath recorded body temperatures as low as $-0.2°$ C. in hibernating marmots that subsequently roused spontaneously (Horvath, 1881). Horvath did not suppose that the animals were frozen. Since then E. F. Adolph and other physiologists have established the lethal body temperatures for adult mammals of a great variety of orders and species, some of which hibernate (Burton and Edholm, 1955). In every instance the result was essentially the same: breathing and heartbeats stopped and the animals died when the internal temperature was still well above the freezing point of plasma.

The report by Bachmetiev in 1912 that hibernating bats survived cooling to body temperatures as low as −9° C. was exceptional, and his theory that animals could survive total freezing of all their body water generally was not accepted. Further studies on cooling bats have been carried out in recent years by Kalabukhov (Kalabukhov, 1934, 1958), who finds that these mammals have a remarkable capacity for becoming supercooled, both under natural and under experimental conditions, particularly when they are immature. Kalabukhov recorded deep body temperatures and electrocardiograms, and demonstrated that the heart continued to beat in bats in the supercooled state. Some of his results are shown in TABLE 1.

TABLE 1
CHANGES IN THE HEARTBEAT IN BATS (*Nyctalus leisleri*)*

State of animal	Body temperature (°C.)	Number of heartbeats per minute
Active	+37.3	420
Dormant	+ 4.1	16
Undercooled	− 4.33	8.5

* Kalabukhov, 1958.

Kalabukhov has succeeded in keeping bats in the supercooled state for several hours and even for days at temperatures between −5° and −7° C. When rewarmed, the animals regained full activity. The presumption is that the heart had continued to beat throughout the period during which the body temperature was below zero. Kalabukhov found that bats that had been frozen extensively did not recover, and emphasized that spontaneous crystallization of ice in supercooled bats was lethal. In the past, the supercooled state has been regarded as highly unstable, and it was thought that vibrations might precipitate freezing which, in any case, would sooner or later occur spontaneously. This view must be revised in the light of the discovery by Scholander and his co-workers (1957) that deep water arctic fish are permanently supercooled by about 1° C. The fish swim around actively and feed themselves throughout the year in the supercooled state, but die if they become seeded with ice crystals and freeze. Supercooled bats are, of course, torpid and their survival probably is limited to the period for which starvation is tolerated by the beating heart and the rest of the organism.

There are other examples in nature of animals that survive in the supercooled state with vital functions slowed but not arrested. I propose, however, to turn to the problem of resuscitating mammals in which the internal temperature has dropped below the freezing point and in which respiration and circulation are at a complete standstill. A few years ago all the scientific evidence suggested that such a project was hopeless. New prospects were opened by R. K. Andjus (1951), who demonstrated that about 20 per cent of adult rats could be resuscitated after 1 hour without breathing or heartbeats at body temperatures just above 0° C. Improvements in the technique of resuscitation at the National Institute for Medical Research resulted in the revival of between 75 and 100 per cent of rats and mice kept in this way. (Andjus and Smith, 1954, 1955; Andjus and Lovelock, 1955; Goldzveig and Smith, 1956*a*). Andjus also found that rats would survive supercooling to several degrees below zero, but not partial freezing, when treated by the methods then in use (Andjus, 1955). It was a particular pleasure to learn three years ago in Washington, D. C., that Niazi and Lewis, working independently and using entirely different methods had resuscitated ice-cold and inanimate rats and also monkeys that had been cooled to temperatures only a little above zero and well below the previously accepted lethal limit at which breathing and heartbeats cease. The behavior of these monkeys, in which cardiac standstill had lasted for up to two hours, apparently was not altered and no neurological abnormalities were detected in the months following reanimation (Niazi and Lewis, 1957). We found by precise psychological tests that rats that had learned to solve problems before cooling showed no significant loss of memory after resuscitation from body temperatures just above 0° C., in spite of complete suppression of spontaneous cortical electric activity for periods of up to 2 hours (Andjus *et al.*, 1955, 1956). The fertility of the rats was reduced soon after reanimation, but a few weeks later reproductive capacity was regained and many normal litters were produced and reared by parents that had been kept for 1 hour with arrested respiration and circulation at body temperatures between 15° and 0° C. (Goldzveig and Smith, 1956*b*).

Golden hamsters, artificially cooled by the method used for rats, were easier to resuscitate. Heartbeats were recorded at colonic temperatures between 2° and 6° C. By the time the internal temperature had reached 12° C. the hamsters were breathing naturally and shivering vigorously and thereafter required no further treatment. Hamsters survived longer periods of suspended animation at 0° C. than rats, and recovered fully after breathing and heartbeats had been at a standstill for 2½ hours. For these reasons hamsters were used to determine whether mammals would survive reduction of their internal body temperature to levels below the freezing point of plasma and tissue fluid (Smith *et al.*, 1954). At this point I must emphasize that, during natural hibernation, breathing and heartbeats do not stop, nor do hibernating mammals of any species studied to date become frozen, because metabolic processes and heat production continue and the animals increase the metabolic rate or else rouse spontaneously when the environmental temperature falls below zero (Lyman, 1948). The physical processes of freezing and thawing are just as unnatural and dangerous for the cells and tissues of the hamster as for those of the mouse or man or any other mammal.

In the first stage of each experiment the hamsters were cooled as before by the closed vessel technique of J. Giaja (Andjus and Smith, 1955). The animals became anesthetized by the combined effects of the falling oxygen and rising CO_2 tensions of the cold atmosphere they breathed and by the resultant fall in body temperature. They were then transferred to baths of melting ice, with the result that the body temperature fell rapidly, passing in about 30 min. from 17° C. to 2.5° C., at which temperature heartbeats, as judged by electrocardiograms, had usually ceased. The inanimate animals were then placed in baths of propylene glycol at −5° C. Within 5 or 10 min. the internal body temperature reached 0° C. and then fell below zero.

In about 25 per cent of the animals the subcutaneous and deep body temperatures continued to fall, as shown in the FIGURE 1*a*, and gradually approached the temperature of the bath which, in some experiments, was reduced from −5° to −8° C. These animals remained soft and unfrozen and were, obviously, in the supercooled state with body temperatures well

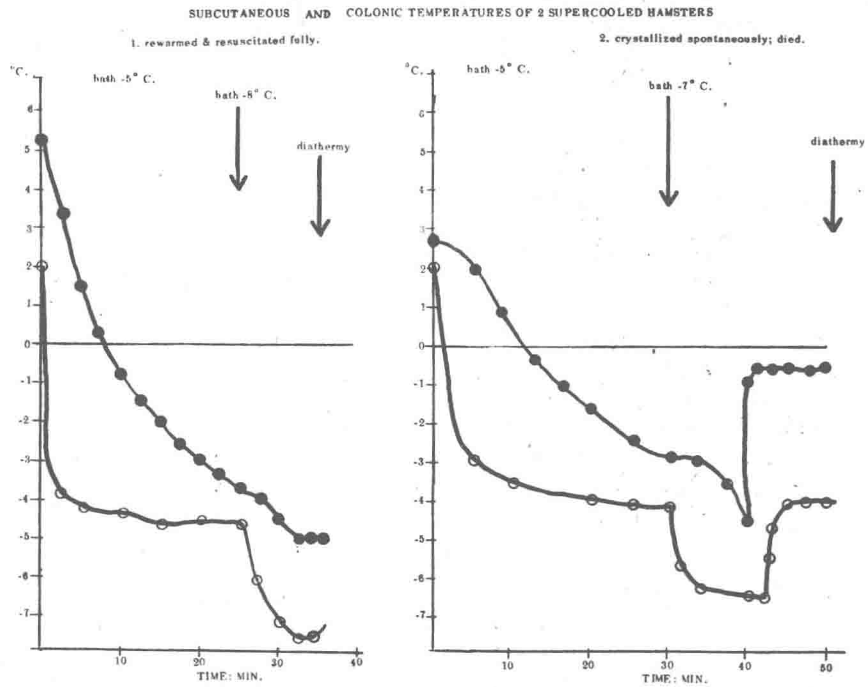

FIGURE 1

below the freezing point of plasma. Supercooled hamsters with internal temperatures as low as −5° C. were resuscitated completely by heating the entire body with diathermy or under bench lamps while artificial respiration was given (Smith *et al.*, 1954).

In some of the supercooled hamsters that apparently had been cooled in exactly the same way, the deep body temperature rose suddenly to a level at about −0.6° C. and soon after the subcutaneous temperature rose to about −2° C. while they were still immersed in fluid at −5° to −8° C. (FIGURE 1*b*). The only possible explanation for this rise in temperature was that freezing had occurred spontaneously and that evolution of latent heat of crystallization had warmed the interior of the body. This explanation was supported by the progressive stiffening of the body which subsequently occurred while its internal body temperature remained at the freezing point of plasma (Smith *et al.*, 1954). When resuscitation was attempted immediately after the onset of crystallization, as judged by the rise of colonic temperature, hamsters that previously had been supercooled to internal temperatures as low as −3.0° C. usually recovered fully, whereas those that had been supercooled to deep body temperatures of between −3.0° and −6.0° C. succumbed,

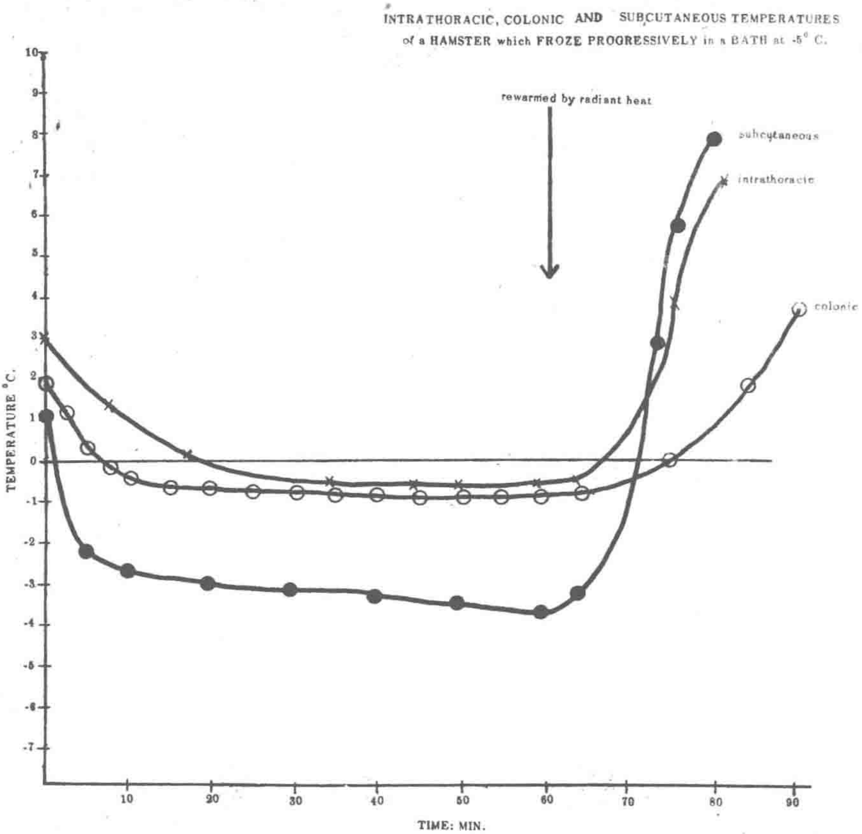

FIGURE 2

although heartbeats and natural breathing were restored temporarily in some instances. When resuscitation was delayed until the previously supercooled animals had been freezing for 10 to 30 min., they seldom showed any signs of revival (Smith, 1956*b*).

By contrast, about 75 per cent of the hamsters began to freeze soon after immersion in the bath at −5° C. The ears and paws began to stiffen perceptibly before the deep body temperature had reached zero. Gradually during the next 30 to 60 min. the whole surface of the animal became rigid while the colonic temperature remained at a level between −0.5° and −0.9° C., as shown in FIGURE 2 (Smith *et al.*, 1954). The intrathoracic and cerebral temperatures reached about the same level, but the subcutaneous temperature fell to between $-2.5°$ and $-4.5°$ C., depending upon the position of the thermocouples (Smith, 1956*a*). Saline and serum froze within capillary tubes that had been inserted into different parts of the body and ice crystals could be seen in the subcutaneous tissues, in the abdominal and thoracic organs, and in the brains of animals that were dissected in the frozen state. Calorimetric determinations showed that after one hour in the bath at $-5°$ C., 40 to 50 per cent of the body water had been converted into ice (Lovelock and Smith, 1956). Nevertheless, a high proportion of hamsters frozen progressively for 40 to 60 min. recovered fully after thawing with diathermy and the administration of artificial respiration. The extremities were not frostbitten unless they had been bent in the frozen state (Smith, 1954, 1956*b*). Although the surface of the body was undamaged, most of the frozen hamsters passed fresh blood per rectum during the first few hours following reanimation and autopsies showed that the site of bleeding was the stomach. A few animals died several weeks later with perforated gastric ulcers. When pregnant hamsters were frozen on the ninth, tenth, or eleventh day of the 16-day gestation period, placental hemorrhages occurred, and many of the fetuses were resorbed. Hamsters frozen for short periods at other stages of pregnancy delivered and reared normal young. However, grossly deformed fetuses were found in some of those frozen for 45 to 60 minutes (Smith, 1957*a*).

I mention these findings partly because of their intrinsic interest for pathologists and embryologists and partly to correct the impression that freezing the whole animal can be regarded as an innocuous process. Even a small rodent as sturdy as the hamster depends greatly on the recuperative powers of the body to repair the damage that occurs while circulation is at a standstill and when water is withdrawn from the blood and tissues by the formation of ice. The hazards of severe hypothermia and of freezing and the need for fundamental studies of the damage to individual organs as well as to the animal as a whole were more obvious when an attempt was made to repeat the experiments on larger mammals (Smith, 1957*b*).

When rabbits 1 to 2 kg. in weight were enclosed in vessels 10 to 20 liters in capacity in a cold room at $-2°$ C. they became comatose after about 3½ hours. The deep body temperature at this stage was 30 to 32° C. The animal recovered after taking several breaths of fresh air and resisted immersion in icy water. Induction of hypothermia was hastened by admitting 3 liters of CO_2 to the box enclosing the rabbits and allowing a corresponding amount of air to escape. Three hours later the respiratory rate was 40/min., and the animals remained comatose after admission of 1 to 2 liters of oxygen. Thirty minutes later the deep body temperature was between 23° and 18° C., and no responses other than the corneal reflexes could be elicited. Rabbits so treated recovered spontaneously in air at $+20°$ C. Others, transferred to icy water, continued to cool very slowly and were still breathing 30 min. later with colonic temperatures between 20° and 14° C. Three animals dried at this stage recovered at room temperature, but one died the next day and another within a week. Rabbits left in melting ice stopped breathing at body temperatures between 18° and 12.0° C. Heartbeats and natural breathing usually could be restored temporarily by rewarming under a radiant heat lamp and giving artificial respiration, but of 6 rabbits kept with breathing and circulation arrested for 20 to 40 min., at body temperatures between 12° and 9° C., only one recovered fully and it died 3 days later. At autopsy the conspicuous abnormality in each instance was a massive gastric hemorrhage.

It seemed possible that less damage would occur after respiratory and circulatory arrest if the interior of the body could be cooled rapidly to a lower temperature and that more efficient methods of rewarming and giving artificial respiration would be needed. The problems involved are dealt with in detail by J. E. Lovelock elsewhere in this monograph. The rate of cooling was increased greatly when the stomach and intestines were irrigated with an ice cream mixture and when the rabbits had been completely depilated, but the gastric and intestinal lesions were intensified and there seemed little prospect of restoring to good health rabbits without any fur. When the abdomen had been shaved and the rest of the fur washed with detergent, the rectal temperature of rabbits immersed in vigorously stirred baths at −5° C. fell from +18° C. to −0.5° C. within one hour of cessation of breathing and heartbeats. By this time the extremities and superficial tissues had been freezing for about 45 min. and the subcutaneous temperature was about −2.5° C. The quantity of ice formed and the energy needed to thaw them was, therefore, much greater than had been required for the hamsters. In early experiments in which diathermy was used, both dielectric and induction heating tended to burn the surface tissues without warming the interior organs of the rabbits. Modifications of technique resulted, at first, in cooking the internal organs. Eventually these hazards were overcome and the frozen rabbits were thawed within a few seconds and the deep body temperature was raised from 0° to +10° or +15° C. in 1 min. The energy input was then reduced so that the colonic temperature rose by 1° to 2° C./min. while cold air was blown over the surface of the body. Fifteen frozen rabbits were treated in this way. In each instance the heart resumed beating when the colonic temperature was about 15° C. and the animals breathed spontaneously at colonic temperatures between 20° and 30° C. They regained corneal reflexes and made spontaneous movements, but collapsed and died within an hour whether or not warming was continued. Autopsies showed that there had been massive hemorrhage from the fundus of the stomach. Microscopic studies showed that bleeding was restricted to regions in which oxyntic cells were present. The pyloric part of the stomach was normal. A similar hemorrhagic lesion occurs in rabbits at normal body temperatures after injections of posterior pituitary extracts (Dodds *et al.*, 1937; Cutting *et al.*, 1937). It is due to intense gastric vasoconstriction and the resultant reduction in volume and increase in acidity of the gastric juice secreted. It can be prevented by neutralizing the gastric contents. We realized that, when circulation was arrested by severe hypothermia, hydrochloric acid would diffuse from the lumen into the wall of the stomach and would erode the blood vessels, just as it does after administration of