

The Current Status of Hypothermia in Cardiovascular Surgery

By HENRY SWAN AND BRUCE C. PATON

IN 1941 Talbott¹ introduced the term "hypothermia" to signify the deliberate reduction in total body temperature of man for therapeutic purposes. However, the term is perhaps most often used to describe the state of a homeothermic animal when its temperature is below normal for that individual.²

Hypothermia must be clearly distinguished from exposure to cold, although the relationship is complex, and exposure to cold is, in fact, a means of obtaining a lowered body temperature. When exposed to a cold environment, the unanesthetized homeothermic animal responds with a number of activities designed to conserve body heat and increase its production, for example: constriction of peripheral vessels and shivering. Eventually, however, the animal becomes exhausted and as heat loss exceeds heat production the body temperature falls. On the other hand, the animal which is adequately anesthetized does not respond with such vigorous efforts to maintain its temperature, the metabolic and circulatory loads are minimized, and its body temperature falls much earlier. Both animals become hypothermic, but the physiologic changes to be observed in such different circumstances vary widely. In clinical hypothermia, the latter type of experience is sought.

No terminology has yet been agreed upon to describe the various degrees of hypothermia, but the following scheme is suggested and will be used in this discussion.

Moderate hypothermia37-28 C.
Intermediate hypothermia28-20 C.
Deep hypothermia20-0 C.
Supercoolingbelow 0 C. <i>without</i> ice formation.
Freezingbelow 0 C. <i>with</i> ice formation.

Moderate hypothermia permits a reduction of metabolism by about 50 per cent without the danger of ventricular fibrillation. If cooling is deepened into the "intermediate" range there is a further reduction in metabolism to about 25 per cent of normal but ventricular fibrillation is almost certain to develop unless inhibited by some specific means. When deep hypothermia is obtained in homeothermic animals spontaneous rewarming becomes impossible and cardiac activity ceases.

Temperatures below 0 C., with and without freezing, have been attained

From the Department of Surgery and the Halsted Laboratory for Experimental Surgery, University of Colorado School of Medicine, Denver, Colo.

The work reported from this laboratory has been supported over the past few years by grants from the American Heart Association, U. S. Public Health Service, and by contracts with the Surgeon General, U. S. Army.

experimentally³⁻⁵ but there is not a recorded instance of a human having recovered after being cooled to this degree.

HISTORICAL ASPECTS

Exposure to cold in the form of cold water or ice has long been used in medical therapy. Hippocrates⁶ observed its analgesic properties and recommended the application of cold water or ice for various injuries, apparently with the opinion that the cold would minimize hemorrhage. In Renaissance times fevers were treated with cold drenching and some of the 17th Century technics for cold hydrotherapy of the pyretic patient have a resemblance to certain methods used in present day clinical practice for the induction of hypothermia (fig. 1).

In 1797 Richard Sutton, Esq. of Liverpool was probably the first patient to undergo therapeutic general hypothermia. His physician, Dr. James Currie,⁷ reduced his temperature to 83 F. by keeping him in a salt water bath for a period of 45 minutes. John Hunter⁸ attempted to freeze and then thaw a carp by surrounding it with melted snow. He saw the slowing down of its activity and was able to freeze the fish and then thaw it out, but although its flexibility was restored, its life was not. In 1862 Walther,⁹ while cooling rabbits to 20 C., made the important observation that artificial rewarming was necessary if recovery from this temperature was to be achieved.

The first major study of the possible clinical value of general hypothermia was undertaken by Smith and Fay¹⁰ in patients with advanced cancer. They kept more than 100 patients moderately hypothermic for up to eight days, and were able to demonstrate conclusively the tolerance of man to prolonged temperature reduction to between 80 and 90 F.

In 1950, Bigelow, et al.¹¹ revitalized this entire field of investigation by demonstrating that dogs could tolerate temperatures of 20 to 25 C. with cessation of the circulation for 15 minutes. This report was a direct stimulus to the advancement of open-heart surgery, and in 1953 Lewis and Taufic¹² reported the suture closure of an interatrial septal defect using hypothermia and the circulatory occlusion. A few months later the first series of patients undergoing open-heart surgery for various congenital defects was reported by Swan et al.¹³ Since then the use of hypothermia alone and more recently the use of hypothermia combined with extracorporeal circulation has resulted in the development of techniques to repair the majority of congenital and acquired cardiac lesions.

PHYSIOLOGY

A. *Tolerance to Cold*

The tolerance of different cells, tissues, and organisms varies widely. Poikilothermic animals can withstand extreme temperatures and some arctic fishes maintain normal activity at temperatures around 0 C. Amongst homeothermic animals there are great differences between hibernators and non-hibernators. Golden hamsters have been frozen at -3 C.⁵ and similar experiments have been performed with non-hibernating rats¹⁴ with cardiac standstill for 40



Fig. 1.—The early days of surface cooling.

minutes with consistent survival, and with standstill for several hours with occasional survival. Cats seldom survive temperatures below 16 C., but Simpson¹⁵ showed that monkeys could be successfully revived from 14 C. However, the safe resuscitation of non-hibernators from very low temperatures depends upon anesthesia at the outset, artificial respiration as the temperature decreases, and a system of rewarming when recovery is desired.

Remarkably little is known about the tolerance of man to extreme degrees of cold. Observations made almost a century ago¹⁶ in an insane asylum where some of the patients ran naked in the cold showed that man can sustain apparently normal activity with a body temperature of 23.7–29.5 C. During

World War II, brutal and inconclusive experiments were carried out by the Germans at Dachau.¹⁷ Unanesthetized prisoners were cooled in ice-water and it was found that the temperature at which half of them died was 27 C. and the lowest temperature recorded was 26.7 C. Death was thought to be due to ventricular fibrillation. Laufman¹⁸ published a fully documented and detailed account of survival following cooling to 18 C. (rectal) in a negro woman. She subsequently lost both legs and nine of her fingers but her cerebral function was unimpaired apart from a period of amnesia.

B. Metabolic Effects

1. *Oxygen consumption.*—The metabolic effect of hypothermia which supercedes all others both in magnitude and importance is a reduction in oxygen consumption. Numerous studies^{19,20,11,21,22,23} have all shown that as the temperature falls the oxygen consumption decreases in a linear fashion. However, if shivering occurs during the early stages the consumption of oxygen is temporarily increased. This can be avoided by adequate anesthesia or by the use of muscle relaxants.

Gordon et al.²² reported the oxygen consumption to be reduced to about 50 per cent of the precooling level at 30 C., to about 25 per cent at 22 C., 12 per cent at 16 C., 6 per cent at 10 C., and 3 per cent at 6 C. with pervascular cooling. The flow rates were approximately 40–90 cc./Kg./min. with a mean of 60 cc./Kg./min. That flow rate under such circumstances is one of the determinants of oxygen extraction at low temperatures was clearly demonstrated by Kameya et al.²³ With high (199 cc./Kg./min.) flow rates, O₂ consumption at 20 C. was 2.1 cc./Kg./min., while at low flow rates (40 cc./Kg./min.), it was only 1.1 cc. Similarly at 10 C. these figures were 1.2 and .7 cc./Kg./min. respectively. In these data, with high flow rates oxygen consumption was reduced at 20 C. to 33 per cent and at 10 C. to 17 per cent of normal, values definitely higher than those of Gordon.²² It is clear in either case, that at 10 C. there remains significant oxygen consumption.

Changes in the oxygen dissociation curve are of critical importance in discussing the level of tissue oxygenation. Brown and Hill²⁴ in 1923 showed that cooling moved the curve upward and to the left. Rosenhain and Penrod²⁵ and Edwards et al.²⁶ believed that in spite of this oxygen transfer to hypothermic tissues since A-V oxygen differences remained constant. However, a constant A-V oxygen difference does not prove that tissue oxygenation was adequate because the venous level might not have been determined by the extraction of oxygen by the tissues but rather by the adherence of oxygen to hemoglobin.

On the other hand, the ability of oxygen to be dissolved in the plasma increases with diminishing temperatures and at 20 C. there is a 50 per cent increase in dissolved oxygen, and between 25 C. and 0 C. the amount of oxygen dissolved in the plasma increases from 2.8 to 4.9 volumes per cent.²⁷ At very low temperatures the amount of oxygen dissolved in the plasma may be sufficient for the minimal metabolic demands of the tissues without invoking the usual mechanisms of oxygen release from hemoglobin.

This may further explain why changes in flow rate, even at low tempera-

tures, influence the total oxygen consumption. With high flow rates greater amounts of dissolved oxygen are presented to the tissues and with low flow rates only minimal amounts of dissolved oxygen are available. It seems evident, therefore, that even at low temperatures (10 C.) high flow rates (60 cc./Kg./ or more) must be maintained if adequate tissue oxygenation is to be achieved.

2. *Acid base balance.*—The estimation of the degree and type of acidosis found at low temperatures is not simple. The simple measurement of plasma CO_2 or pH does not give a genuine picture of the acid base balance during changes of temperature. Unless the pH and pCO_2 are measured at the actual temperature of the blood, the factors defined by Rosenthal²⁸ should be used to correct the results. The use of these correction factors may under some circumstances show that an apparent tendency to acidosis is, in fact, an alkalosis. The importance of these correction factors has only recently been receiving wide acceptance²⁹ but results interpreted without their use may be almost meaningless.

Because both metabolic and respiratory factors play a significant part in influencing the acid-base balance an exact knowledge of the state of respiration during hypothermia is important in the interpretation of pH changes. If cooling is permitted without assisted respiration a respiratory acidosis develops as the efficiency of ventilation diminishes. At the same time more CO_2 is dissolved in the plasma at lower temperatures affecting the plasma pH, although this change is offset by a decreased peripheral production of CO_2 and an increased carrying capacity of the blood for CO_2 (as bicarbonate).

In patients and experimental animals it has been found that a metabolic acidosis may develop³⁰ especially in the rewarming period³¹ and an "acute acidotic syndrome" at this time has been described.³²

In the clinical application of deep hypothermia, acidosis has not presented a significant problem.³³ However, experimental work³⁴ has shown that a significant acidosis can occur even at low temperatures. This acidosis is probably more marked with core-induced hypothermia than with general hypothermia. This may be due of the temperature gradients which occur between various tissues and organs and the blood with this type of hypothermia (fig. 2). As a result of these gradients considerable masses of tissue, such as muscle, may be perfused by blood with a temperature 10 to 15 C. lower than that of the tissue itself. Thus an organ at 25 to 30 C. may be perfused by blood at 10 to 15 C. and be in the disadvantageous situation of needing 40–50 per cent of its normal oxygen requirement yet be unable to extract that oxygen from the blood. It is not surprising that under these circumstances organs resort to anaerobic metabolism and a metabolic acidosis results.

3. *Fluid shifts.*—A consistent increase in hematocrit during hypothermia has been noted by numerous observers^{13,35-38} and this change has been accepted as an indication of diminution in plasma volume during the cooling phase. The decrease in plasma volume is usually around 10 per cent or less, and changes in the plasma specific gravity and plasma proteins commensurate with the alterations in hematocrit and plasma volume have also been observed. As with many of the other physiologic changes induced by hypo-

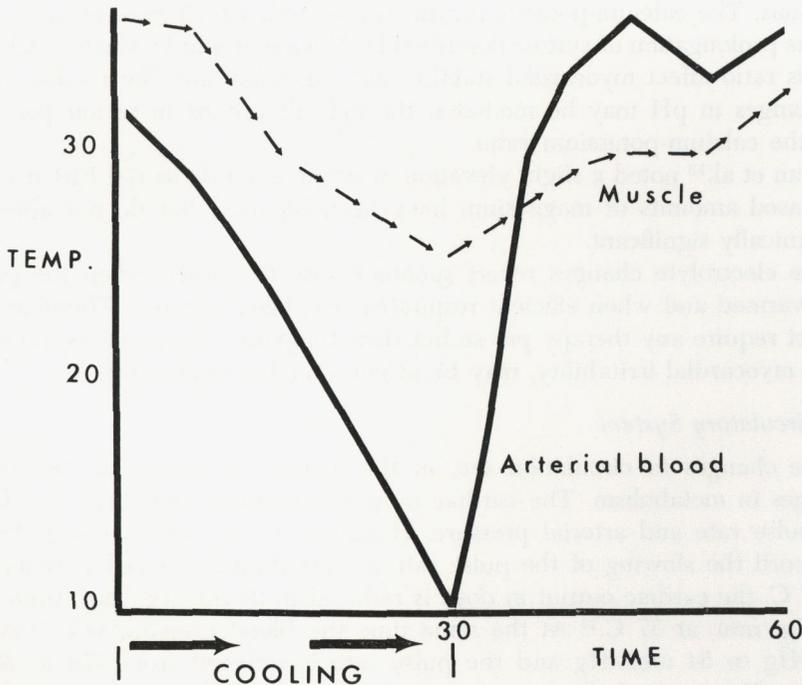


Fig. 2.—Temperature gradients between arterial blood and muscle. It can be seen that muscle at 25 C. is being perfused by blood at 10 C.

thermia those in the plasma volume revert to normal when the patient is rewarmed.

The clinical use of hypothermia does not therefore by itself require any changes in the usual management of fluid balance, except that the infusion of glucose is probably desirable for other reasons.

4. *Electrolyte changes.*—Considerable discussion occurs in the literature concerning the changes in the levels of individual electrolytes during hypothermia. The reasons for the discrepancies reported are not always clear but may well be related to the varying cooling technics and types of anesthesia used in the different studies.

Sodium levels in the plasma do not change or show a slight decrease. Wynn³⁹ showed that in the presence of intravenous infusions of 5 per cent glucose a significant dilution of the extracellular fluid might cause hyponatremia, because the delay in metabolism of the glucose results in an osmotic dilution of the plasma.

The greatest variations in findings have concerned potassium. Several investigators have noted an elevation of serum potassium,^{11,40,41} while others noted a fall in the serum potassium level.^{13,31,42} There seems little doubt that these differences of opinion do not reflect incompatible observations but rather observations made under different circumstances. Swan et al.¹³ showed that serum potassium levels varied with the pH and bicarbonate and a reciprocal relationship exists between the serum pH and the potassium level.

The amount of serum calcium increases⁴¹⁻⁴³ both in the ionized and bound

fractions. The calcium-potassium ratio is elevated, which may be responsible for the prolongation of systole described by Hegnauer and D'Amato.²¹ Changes in this ratio affect myocardial stability and efficiency and the cardiac results of changes in pH may be mediated through alterations in serum potassium and the calcium-potassium ratio.

Swan et al.¹³ noted a slight elevation in serum chloride as did Fisher et al.³⁸ Increased amounts of magnesium have been reported but do not appear to be clinically significant.

The electrolyte changes revert spontaneously to normal when the patient is rewarmed and when efficient respiration has been restored. Therefore they do not require any therapy per se but their temporary local effects, especially upon myocardial irritability, may be of considerable importance.

C. Circulatory System

The changes in circulation are, in the main, proportional to the overall changes in metabolism. The cardiac output is reduced and there is a fall in the pulse rate and arterial pressure. Hamilton et al.⁴⁴ were among the first to record the slowing of the pulse rate in cats during induced hypothermia. At 17 C. the cardiac output in dogs is reduced to 26 ml./Kg./min. from 145.5 ml./Kg./min. at 37 C.²¹ At the same time the blood pressure falls from 126 mm./Hg to 54 mm./Hg and the pulse rate is reduced from 170 to 26 per minute. However, if shivering is permitted while cooling is being induced, there is a rise in cardiac output and arterial pressure. Hypertension may also be noted during hypothermia immediately following the release of circulatory occlusion.⁴⁵

Venous pressure may rise during the period of cooling, and always does so during a period of circulatory occlusion. The increase in pressure during the cooling period may be due to positive pressure respiration; the elevation during the period of circulatory occlusion may be due to increased venous tone limiting an increase in capacity of the venous reservoir.

The total peripheral resistance increases and this is probably due to a simultaneous increase in viscosity of the blood together with an increase in vascular tone. Direct observation of the capillaries⁴⁶ has suggested that increased viscosity with aggregation of red cells may be the more important factor. Gelin⁴⁷ considered that the use of low molecular weight dextran as a diluting infusion might favorably decrease the viscosity and showed experimentally that this diminished the amount of red cell aggregation. Clinical confirmation of this concept has been obtained by Long⁴⁸ and his associates who observed the conjunctival capillaries during operation and saw a favorable decrease in sludging after the use of low molecular weight dextran.

In spite of these factors, during short periods of hypothermia, circulation appears to be adequate to all parts of the body.

The effects of hypothermia on the heart are of vital importance. Cardiac work is reduced. In vitro experiments show that the oxygen consumption of isolated muscle slices is reduced in a linear fashion,⁴⁹ and in vivo observations have shown that the heart remains capable of extracting adequate amounts of oxygen for its needs even at low temperatures.³⁶ Coronary flow is reduced⁵⁰

but this reduction is not proportionately as great as that in the systemic circulation.

Myocardial function as judged by pressure contour tracings⁵¹ remains adequate although there is a marked prolongation of systolic contraction and isometric relaxation.^{35,51} Attempts to increase the heart rate artificially under these circumstances of reduced diastole result in cardiac failure.

With progressive cooling, the electrocardiographic changes consist sequentially of bradycardia, prolongation of the P-R interval and QRS complexes, changes in the ST segments and T waves, premature contractions, ventricular fibrillation, and finally cardiac standstill.⁵² Osborn⁵³ in 1953 described some characteristic changes in the ST segments, as a "current of injury" to which he attached serious prognostic significance as a premonitory sign of ventricular fibrillation. However, Emslie-Smith⁵⁴ later showed that these changes are constantly found in all cases of hypothermia and are not necessarily of serious significance.

One of the main hazards in the use of hypothermia is ventricular fibrillation. Not only is its incidence greater under hypothermia than normothermia but it is more resistant to conversion to normal rhythm.⁵⁵

The precipitating factors and possible underlying causes are numerous.

Cold.—It is natural to consider the reduction in temperature per se as a possible cause, but in the analysis of this factor a distinction must be drawn between myocardial excitability and irritability. Hegnauer and Angelakos⁵⁶ showed that a reduction in temperature decreases cardiac excitability but also lowers the fibrillation threshold and increases cardiac irritability. This finding certainly makes more comprehensible the observations of numerous other investigators that a great variety of stimuli can induce fibrillation during hypothermia.

Both experimental and clinical experience has shown that ventricular fibrillation is less likely to occur when the temperature is kept above 28 C.

Hypoxia.—During periods of venous inflow occlusion with simultaneous clamping of the aorta myocardial hypoxia develops and if the occlusion is prolonged beyond 6 minutes the incidence of fibrillation increases.^{57,58}

Electrolyte Changes.—Local changes in myocardial electrolyte levels may be significant, particularly alterations in potassium and calcium. Montgomery et al.⁵⁹ felt that there was a shift of potassium into the myocardial cell during the prefibrillatory stage in animals that were acidotic. This was considered to be an important precipitating factor in the onset of fibrillation. This conception has since been denied by Covino et al.⁶⁰ who found that potassium left the cell. The precise level of intracellular potassium may not be as important as the calcium-potassium ratio⁴¹ and since several observers have noted elevations in calcium during hypothermia, alterations in this ratio are likely.

pH.—The acidosis which occurs during hypothermia is probably important as an initiating or precipitating factor^{56,61} and its avoidance by hyperventilation reduces the incidence of fibrillation.⁶¹ However, Niazi and Lewis⁶² believe that the intentional use of high concentrations of CO₂ in the respiratory gas mixtures prevents the development of fibrillation. This apparent paradox is probably because neither high nor low pH's by themselves affect the in-

cidence of fibrillation, but the maintenance of a steady pH without sudden changes during cooling or rewarming is the most important feature to be attained. However, increasing $p\text{CO}_2$ moves the oxyhemoglobin dissociation curve to the right and downwards thereby increasing the efficiency of oxygen extraction from the blood which may be important in preventing myocardial hypoxia and subsequent fibrillation.

Venous Pressure.—Bigelow¹¹ was unable to prevent or treat ventricular fibrillation by any electrical or mechanical means except by reducing the inflow pressure which builds up during the period of circulatory occlusion.

Autonomic Nervous System.—Montgomery et al.⁵⁹ demonstrated that ventricular fibrillation could be prevented by the intracoronary injection of neostigmine, an anticholinesterase agent. Stimulation of the peripheral end of the cut vagus produced a similar salutary effect. Shumacker et al.⁶³ and Navratil⁶⁴ both showed by different means that blockage of sympathetic impulses inhibited the development of ventricular fibrillation.

Mechanical Stimuli.—Hegnauer et al.⁶⁵ showed that the mere presence of an intraventricular catheter increased the likelihood of fibrillation, and countless observations at the operating table have confirmed that mechanical stimuli of any sort may set off ventricular fibrillation in an irritable heart.

Epinephrine.—During hypothermia increased amounts of epinephrine and norepinephrine circulate in the blood.⁶⁶ Since Berne in 1954⁵⁰ had shown that injected epinephrine may stimulate the onset of ventricular fibrillation this increased level of endogenous catechol amines may be important.

Anesthetics.—Cyclopropane⁶⁷ has been incriminated as an influence in the production of fibrillation especially when combined with epinephrine. Pentothal is thought less likely to produce fibrillation than Nembutal, but most of the anesthetic factors concerned with the development of fibrillation are ventilatory rather than pharmacologic.

Management of Ventricular Fibrillation

Prevention.—Many antifibrillatory drugs have been recommended. Neostigmine was first suggested by Montgomery.⁵⁹ One to two cc. of a 1:4000 solution is injected into the root of the cross-clamped aorta to perfuse the coronary arteries. This both slows the heart during the period of occlusion and protects against fibrillation. The use of quinidine was reported by Gollan,⁶⁸ Berman et al.⁶⁹ Angelakos⁷⁰ and Johnson et al.⁷¹

Antihistamines, local anesthetics and tranquilizers have all been tested but none has attained general clinical acceptance.

Both hyperventilation⁶¹ and the use of high concentrations of CO_2 in the respiratory gas mixture⁷² have been advised and the rationale of those methods has been discussed above. They are both effective.

Intravenous nutrient solutions such as dextrose, glycine, dextran, and fat emulsions have been shown by Caranna et al.⁷³ to decrease the incidence of fibrillation in dogs cooled to 23–25 C. and subjected to cardiac incision. Not only was the incidence of fibrillation less in these animals but when it occurred resuscitation was easier.

Perfusion of the coronary arteries during the period of circulatory occlu-

sion has been advised by Shumway et al.⁷⁴ and Edwards et al.²⁶

Infiltration of the atrium and the S-A node with procaine has been tried but again this method has not become generally accepted.⁷⁵

D. Central Nervous System

The important questions concerning the relationship between hypothermia and the central nervous system are these: (1) what is the lowest temperature which can be tolerated? (2) What is the effect of hypothermia on cerebral, cord, and nerve function? and (3) how long will the cord and brain tolerate complete cessation of circulation at various temperatures?

The data concerning the pathology of cold in the central nervous system, are conflicting. Parkins et al.⁷⁶ found serious brain damage with differential cold perfusion when the brain temperatures of dogs were lowered below 14 C. On the other hand, Adams and Pevehouse⁷⁷ achieved survival without neurologic damage in dogs cooled to 12 C. brain temperature by regional perfusion. Niazi and Lewis⁷⁸ cooled dogs by immersion to 7 C. with recovery without brain damage, and more recently, Gordon and Jones et al.²² using pervascular cooling achieved cerebral temperatures of 8–12 C. without damage. It appears, therefore, that cooling to temperatures as low as 8 C. by this technic, does not result in pathology in dogs. As regards man, certain patients in Temple Fay's series¹⁰ who succumbed had been subjected to temperatures down to 25 C. for as long as 150 hours. A study of these brains by Sano and Smith⁷⁹ did not reveal any pathology.

Peripheral neurological lesions have been observed in both animals and humans cooled by ice-water immersion⁸⁰ when exposure to the ice-water was prolonged. In three cases measured, the temperature of the extensor muscle mass of the forearm fell to 3–5 C. This confirms the experimental work of Denny-Brown et al.,⁸² who demonstrated peripheral nerve lesions below 8 C. Recent clinical experiences with profound hypothermia have revealed the possibility of severe cerebral damage arising some days or even weeks after the patient has been cooled.⁸¹ The syndrome produced by these changes consist of Parkinsonism and progressive cerebral deterioration to the time of death. It is thought that microscopic aggregations of red cells and white cells in the cerebral capillaries result in micro-infarcts, and these lesions seem to be more common in children than in adults. For this reason Bjork⁸¹ advises against the use of this technic in children.

Hypothermia has a significant depressant action on brain and nerve function, and because of this depressant action, hypothermia is an effective method of producing anesthesia.⁸³ Electroencephalography shows that voltage amplitude begins to fall between 32–34 C. until the level of electrical silence is reached at 18–20 C.⁸⁴ Blair et al.⁴⁵ in a study of humans undergoing cardiac surgery during hypothermia, found that the cardiovascular reflexes remained intact down to about 27 C.

How protective is hypothermia against the damage of anoxia or ischemia? Evidence from dogs,⁸⁵ cat brain slices in vitro⁸⁶ and humans⁸⁷ confirm that cerebral oxygen consumption decreases linearly with temperature. Loughheed and Kahn⁸⁸ found that at 30 C., the cerebral metabolic rate of dogs was re-

duced to 50 per cent, and at 25 C. to 25 per cent of normothermic control. At the latter temperature, 7 dogs underwent a 15 minute circulatory occlusion with survival. As a result of these studies, Loughheed et al.⁸⁸ occluded the cerebral circulation in 2 patients for periods up to 140.5 minutes without evidence of cerebral damage.

Gordon²² found that dogs cooled to 13–18 C. tolerated 25–35 minutes of circulatory arrest without damage. A second group cooled to 8–12 C. similarly tolerated 55–60 minutes of arrest. The oxygen consumption was studied at various temperatures, and using the hypothesis that each 50 per cent reduction in oxygen consumption doubles the safe period for circulatory arrest, the authors constructed the following table:

Temperature	Oxygen Consumption	Safe Period For Circulatory Occlusion
37 C.	100%	4–5 min.
29 C.	50%	8–10 min.
22 C.	25%	16–20 min.
16 C.	12%	32–40 min.
10 C.	6%	64–80 min.
6 C.	3%	128–160 min.

That these periods of circulatory arrest are in fact reasonable was borne out by experimental circulatory occlusions of one hour in dogs at 10 C. In patients at similar temperatures, occlusions of over one hour were not followed by either electroencephalographic or neurologic evidence of central nervous system damage.

The protection afforded by hypothermia to the spinal cord when the thoracic aorta is clamped has been amply demonstrated by Pontius et al.⁸⁹ Owens et al.⁹⁰ and Parkins et al.⁷⁶ A two- to three-fold increase in tolerable periods of aortic-clamping without hind-limb paralysis was demonstrated at temperatures in the range of 23 to 26 C. and at the University of Colorado hypothermia to 30 C. is routinely used in all operations for coarctation of the aorta.

Hypothermia also has a role in the prevention and treatment of brain injury. Rosomoff et al.⁹¹ clearly showed in the dog: 1) that hypothermia of 25 C. for 1 hour markedly reduced the mortality of a standard brain injury; 2) that if hypothermia were instituted within three hours of the injury, a similar protective effect was noted, and 3) the mode of action did *not* appear to be because of reduction in cerebral edema. Clinically, the use of hypothermia in treating patients with severe head trauma has gained widespread acceptance, although the value of the method is difficult to prove. However, Williams and Spencer⁹² demonstrated the advantage of cooling patients who do not immediately recover neurologic function following cardiac arrest and resuscitation. This practice has now become standard treatment under these conditions.

E. Respiratory System

Hypothermia depresses spontaneous respiration, and if the temperature is reduced sufficiently apnea ensues. The exact point at which this occurs de-

depends upon factors such as the type and depth of anesthesia but is usually around 28 C. Because of the diminishing respiratory efficiency and for other metabolic reasons, assistance to the respiration during the induction of anesthesia is desirable. No significant pathology of the lung has been identified as being caused by short term hypothermia alone.

F. *Endocrine System*

Hypothermia is accompanied by a marked depression of adrenal cortical secretion in the dog.^{93,94} The secretion of ACTH and the ability of the cortex to respond to exogenous ACTH are both diminished. Swan et al.⁹⁵ found that major operative stress did not cause elevation of plasma steroids in hypothermic patients. Both conjugation and excretion were simultaneously depressed, but, upon rewarming, adreno-cortical secretion was promptly resumed at a level reflecting the magnitude of the surgical trauma. Thus, as regards the body response to surgical trauma *inflicted* during the cold state, hypothermia appears merely to "stop the clock" temporarily, and on rewarming the usual responses are obtained.

G. *The Kidney*

Most observers⁹⁶⁻⁹⁹ have observed that renal blood flow and glomerular filtration rate are depressed. Total urine volume remains almost normal. The ability of the kidney to produce ammonia or to acidify urine decreases with temperature, but these functions return slowly to normal in the 24 hours following rewarming.

Hypothermia protects the kidney from ischemic damage and the use of local hypothermia by packing the kidneys with ice-bags results in a significant prolongation of the time during which a kidney may be totally ischemic and yet recover its normal function. Nevertheless, patients undergoing resections of aortic aneurysms under hypothermia sometimes show a significant depression of renal function post-operatively which may never return to normal.

H. *The Liver*

Hepatic blood flow is diminished during hypothermia but this does not seem to give rise to sequelae unless the period of hypothermia is prolonged beyond 6 hours when there is some depletion of liver glycogen. Bernhard et al.¹⁰⁰ showed that dogs were able to survive severe ischemia of the liver if they were hypothermic, and for this reason, during hepatic operations requiring prolonged clamping of the portal vein or hepatic artery hypothermia provides protection to the liver. Moore¹⁰¹ observed that livers excised for transplantation would maintain normal viability for 12 hours at temperatures of 20-22 C.

I. *The Clotting Mechanism*

Studies of the clotting mechanism in the dog bear so little relation to the results obtained from humans that they will not be discussed here. Bunker and Goldstein¹⁰² measured various clotting factors in 10 patients undergoing neurosurgical procedures and concluded that with the exception of a sig-

nificant reduction in prothrombin consumption, the changes in coagulation seen were similar to those observed during surgery and transfusions at normal temperatures.

Von Kaulla and Swan¹⁰³ in a study of 11 patients undergoing cardiac surgery during hypothermia, did not observe any bleeding tendency due to prothrombin deficiency. Moreover, bleeding times were not prolonged, nor were platelets significantly depressed. However, thrombin inhibitor was increased and it was believed that such changes were associated with vascular responses predisposing to hemorrhage. In any event, hemorrhage was one of the causes of death in the University of Colorado series as reported by Swan and Blount.¹⁰⁴

Of perhaps equal importance is the possibility of hypercoagulability occurring in the postoperative period. Whether this is true "hypercoagulation" or merely the same tendency to thrombo-embolic episodes which is seen after major surgery at normal temperatures is known. Nonetheless, 4 of Bunker and Goldstein's¹⁰² patients suffered postoperative thrombosis, and pulmonary artery and cerebral thrombosis during the postoperative period was a lethal complication in four patients in the series of 111 patients undergoing intracardiac surgery by Swan and Blount.¹⁰⁴

For these reasons, fresh blood is used for the first two transfusions given during hypothermic cardiac surgery in an attempt to restore to normal any deviations in the clotting mechanism. In addition, adult patients with interatrial septal defects who have a very sluggish pulmonary circulation postoperatively because of the tremendous size of their pulmonary vascular tree are started on heparin when the chest tubes cease draining, and are continued on anti-coagulant therapy for several weeks.

METHODS OF COOLING

Surface cooling has become a standard technique for the induction of moderate hypothermia. As used in the University of Colorado hospitals, the following method is uniform procedure. Very similar technic is used by Bigelow¹⁰⁵ in Toronto, Brom¹⁰⁶ in Leiden, Zindler¹⁰⁷ in Dusseldorf, and Sellick¹⁰⁸ in London.

1. The rectal temperature is reduced to 30–32 C. This is the lowest level reached after drift, and every effort, including the use of diathermy, is made to prevent the temperature from falling below 30 C.⁵⁸

2. Cooling is achieved by immersion in ice water. The patient, premedicated by Demerol (meperidine) or a barbiturate and small doses of scopolamine (not morphine or atropine), is anesthetized to the second surgical plane with ether. He is then immersed in a tub containing luke warm water. When all vital signs appear stable, cubes of ice (about 50 to 75 lbs. for an adult) are added to the tub. The water is constantly stirred. An adult may take 30 to 60 minutes, and a small child 8 to 12 minutes to cool to 33 C. (rectal), at which temperature he is removed to the operating table. The end temperature will be about 30–30.5 C. with this method. After removal from the tub the patient's skin is carefully dried and powdered and the diathermy coil attached around the pelvis.

3. Throughout the induction, the course of cooling, the operation and the recovery period, deliberate respiratory alkalosis is maintained by hyper ventilation.⁶¹

4. During the procedure, a constant drip of 5 per cent dextrose is maintained at 30 to 40 drips a minute. A deliberate hyperglycemia is thus achieved. A beneficial effect of intravenous nutrients on the myocardium during hypothermia now appears to be confirmed.⁷³

5. The first two pints of blood used for transfusion are freshly drawn, heparinized in siliconed bottles. The presence of platelets, fibrinogen, and other enzyme elements of the clotting mechanism together with absence of citrate, are considered to be helpful in avoiding the bleeding diathesis formerly seen in hypothermia.¹⁰⁴ A low blood volume is scrupulously avoided as hypovolemia is poorly tolerated by the hypothermic individual.¹⁰⁹

6. The patient is rewarmed by internal heating, i.e., diathermy, applied to the pelvis and he must be breathing spontaneously and responsively before being returned to the recovery room. Careful drying of the skin, padding, and only intermittent use of the diathermy are essential to avoid burns of the sacral area.

Other agents besides ether, including chlorpromazine, barbiturates, paraldehyde, curare, and opiates have been used to suppress the shivering incited by the stimulus of cold. The "lytic cocktail" does not appear to have advantages over other agents.

Other methods in common use for surface cooling include the temperature control blanket,^{110,111} cold saline intrapleurally,¹¹² ice bags,¹¹³ and cold air chambers.¹¹⁴ These have the disadvantage of taking longer than ice-water immersion. Warming may be assisted by warm blankets, hot water bottles, temperature-control blankets, and warm water immersion, as well as diathermy.

An entirely different extracorporeal technic was suggested almost simultaneously by Boerema et al.¹¹⁵ and Delorme.¹¹⁶ This consisted of allowing the arterial pressure to push the animal's heparinized blood through a heat exchanger and reinfuse it into a vein, and Gollan et al.¹¹⁷ and Pierce and Polley,¹¹⁸ suggested the use of a pump-oxygenator in a veno-arterial cooling circuit. Brock and Ross¹¹⁹ developed a vein-to-vein technic for extracorporeal cooling for clinical use with a hand-driven rotor pump to drive the blood through the heat exchanger. Dogliotti and Ciocatto¹²⁰ first suggested the clinical application of the combined methods of extracorporeal circulation and hypothermia and this technic was later developed and extensively employed by Young, et al.¹²¹ using the improved heat exchanger of Brown et al.¹²² This system has been used successfully for the induction of all degrees of hypothermia. Urschel et al.¹²³ Osborn et al.¹²⁴ and Gebauer¹²⁵ created very effective heat exchangers out of their rotating disc oxygenators, thus not requiring an additional cooling unit in the circuit.

Most recently, Drew et al.¹²⁶ and Shields and Lewis¹²⁷ almost simultaneously reported a technic for achieving deep hypothermia by perfusing both the systemic and pulmonary circuits, using the animal's own lungs for oxygenation and a heat exchanger on the systemic side. Core temperatures in the 10–20 C., range were achieved, allowing periods of complete circulatory occlusion up

to 50 minutes with recovery. Drew and Anderson¹²⁸ described the first patients to undergo this type of cooling for cardiac surgery and many others have continued to explore this method for the repair of a variety of congenital defects.

A final method of cooling which has received clinical trial was described by Parkins et al.⁷⁶ This consisted of perfusion of the brain with very cold blood. Although the rectal temperature remained near 30 C., brain temperatures of 18–20 C. allowed circulatory occlusion for periods up to 30 minutes with recovery. Kimoto et al.¹²⁹ described 5 patients in whom this method was employed for repair of congenital cardiac defects. Their longest occlusion period was 13 minutes.

COMPLICATIONS OF HYPOTHERMIA

The complications of external cooling can be largely prevented, but continuous caution and careful attention to detail must be maintained.

1. Peripheral nerve paralysis may occur as the result of prolonged immersion and may be avoided by not allowing the arms or legs to remain in the ice-water for longer than 30 minutes. Recovery is almost always complete.

2. Burns of the sacral area or around the electrocardiograph needles are distressing, and may cause undesirable morbidity. The former is a lesion due to ischemia from the pressure of the body weight combined with diathermy heat; the latter is probably a complication of the use of electrocautery. Since these burns are deep and the healing slow, early grafting is usually indicated.

3. Ventricular fibrillation is most dangerous if it occurs in a patient not undergoing a thoracic operation. Various agents may be of protective value as discussed above. If the chest is open, electrical defibrillation is almost universally successful.

4. Postoperative hemorrhage occurs more frequently, we believe, than in normothermic patients. This is not due so much to any change in the clotting mechanism caused by hypothermia, but rather to the fact that the wound is made and closed when the blood pressure is depressed. Upon warming, small arterial bleeders not previously manifest, may open up. Meticulous hemostasis in making the incision is thus imperative, and warming the patient on the table with diathermy so that the blood pressure rises before the incision is closed is also helpful. There should be no hesitation in re-exploring to find and ligate the bleeding points as soon as it becomes evident that blood loss is continuing at an excessive rate postoperatively.

5. Gastric dilatation in the immediate postoperative period must be watched for, and intubation resorted to if necessary.

6. Pulmonary complications such as atelectasis or pneumonitis occur with about the same frequency as in thoracic procedures done during normothermia. Hypothermia does not seem to predispose the patient to respiratory infections.

INDICATIONS FOR HYPOTHERMIA

Hypothermia reduces metabolic rate, slows the heart, and causes hypotension. Based on these physiologic effects, some potential uses of this modality are suggested below. It must be noted that some of these have actually been

demonstrated to have merit, while others remain to be investigated. Those which have already had clinical endorsement are marked by an asterisk.

- I. To reduce oxygen need in acute or reversible conditions causing general or local hypoxia.
 - A. Acute pulmonary diseases (atelectasis, pneumonia).
 - B. Pulmonary or cerebral embolus.
 - *C. Post-Cardiac arrest encephalopathy.
 - *D. Acute head trauma.
 - *E. Deliberate temporary interruption of blood supply.
 1. Total interruption.
 - *a. Cardiac Surgery.
 2. Regional Interruption.
 - *a. Descending aorta.
 - *b. Cerebral arteries.
 - *c. Hepatic vessels.
 - *d. Renal vessels.
 - *F. Ischemic extremity.
- II. To cause "physiologic" hypotension and/or local hemostasis.
 - A. To diminish hemorrhage.
 - *1. Brain surgery.
 2. Skin grafting.
 - *3. Gastro-duodenal hemorrhage.
 - B. To counteract hypertensive crises.
 1. Encephalopathy.
 2. Eclampsia.
- III. To increase tolerance to hypotension.
 - A. Septic shock.
 - B. Myocardial infarction.
- IV. To combat hyperpyrexia.
 - *A. Thyrotoxicosis.
 - B. Third-ventricle hemorrhage.
 - C. Heat stroke.
 - *D. Any febrile illness.
- V. To decrease anesthetic or operative risk.
 - *A. In presence of cardiac disease.
 1. Tachycardia (slows heart rate).
 2. Cardiac dilatation (mitral, etc.) - (lower cardiac output)
 - *B. Liver disease (cirrhosis).
 - *C. Chronic pulmonary disease.
 - *D. Any debilitated patient.
- VI. To help combat infection.
 - A. Septicemia.
 - B. Peritonitis.
- VII. Burns.
- VIII. The transplantation of tissues.
 - A. Kidney.
 - B. Liver.

- C. Gastro-intestinal tract.
- D. Skin.
- E. Arteries.
- F. Cornea.
- G. Bone.
- H. Other.

HYPOTHERMIA AND INFECTION

It has been shown that many of the elements of inflammation such as hyperemia, edema, leukocytosis, and local necrosis may be markedly reduced by the use of hypothermia.^{130,131} At the same time, the proliferation of some organisms including strep. hemolyticus is greatly retarded. Eiseman et al.¹³² suggested that the invasive properties of the organism were retarded more than the defense mechanisms of the host, and Fedor et al.¹³³ reached a similar conclusion that ". . . the rationale for the use of hypothermia in combatting infection is reasonable." The clinical trials of this method have as yet been limited.

HYPOTHERMIA AND SHOCK

Does the hypothermic individual tolerate hemorrhagic shock better or worse than the normothermic? The evidence is conflicting.

One of the simpler, more definite relationships is the effect of cold in limiting surface hemorrhage or regional edema. This property has been known since the times of Hippocrates. Duncan and Blalock¹³⁴ found in crushed extremity experiments that the application of ice resulted in less swelling and increased survival if it were maintained throughout the compression period. If the leg were crushed and ice applied thirty minutes later, there was little or no effect. More recently, Willman and Hanlon¹³⁵ clearly demonstrated that hemorrhage from a split-thickness graft site was less when cold compresses were applied. Thus, to whatever extent hypothermia, either regional or general, decreases blood loss or plasma extravasation in the injured individual, to that extent it is beneficial in preventing hypovolemic shock.

Wilson et al.¹⁰⁹ studied the response of dogs to a rapid arterial hemorrhage of 35 per cent of the measured blood volume. Such animals lived if bled when normothermic; but, if bled when hypothermic, only 18 per cent survived. In other words, a certain hemorrhage which killed no warm dogs, killed 82 per cent of hypothermic dogs.

On the other hand, the apparent benefit of hypothermia in the *treatment* of septic shock is mentioned elsewhere in this paper.

It is obvious that much remains to be learned concerning the relationship of hypothermia to shock-like states of various kinds.

SURGICAL USES OF MODERATE HYPOTHERMIA

A. As a *Technic for Open-Heart Surgery*

Certain fundamental technics for open-heart surgery have been evolved.⁵⁸ The patient is very carefully positioned so that the cardiotomy will be at the most superior aspect of the heart. Thus, for closure of an auricular defect the

patient is tipped to the left with head elevated; for pulmonary valve surgery to the right with head markedly elevated; etc. The air may thus escape from the uppermost chambers of the heart through the cardiotomy at the time of retreat from the heart.

At the onset of circulatory occlusion, the heart is slowed by the injection of 1:4000 neostigmine given by coronary perfusion. From 1–2 cc. of this solution will slow but not stop the hypertrophied heart. The heart will stay pink almost throughout the occlusion period, and will resume its beat readily once coronary circulation is allowed.⁵⁹

The root of the aorta is always clamped (except with aortic stenosis) in order to prevent coronary blood flow during occlusion. This helps prevent coronary air embolism, maintains the bradycardia, and in diminishing the coronary return to the heart insures a dry operative field and thus a shorter occlusion period.¹³⁶

The period of circulatory occlusion should not exceed six minutes and *must* not exceed eight. If it is apparent that the complete operation cannot be accomplished in this period of time, the procedure should be stopped and escape from the heart effected, bringing out the loose ends of any unfinished sutures. Circulation is restored. After 10 or 15 minutes to allow re-establishment of normal myocardial metabolism, the occlusion may be repeated. At least 10 to 12 safe minutes of intracardiac time may thus be achieved.⁵⁸

1. *Isolated pulmonary stenosis*.—The results of transventricular instrumental incision and dilatation of the congenitally stenosed pulmonary valve, although often quite satisfactory, have nevertheless frequently been disappointing when objective postoperative studies were performed. The stenosis has been found, at times, to be essentially unrelieved.¹³⁷ Under direct vision during cessation of circulation, the pulmonary artery may be opened, the fused funnel-like valve incised in three directions all the way to the ring. The heart is allowed to fill with blood as the clamp is replaced on the pulmonary artery. The incision in the artery may then be sutured while circulation proceeds.

The results of this operation are eminently satisfactory when studied later by objective measurements. The gradient from right ventricle to pulmonary artery is reduced to less than 20 mm./Hg in almost every case, and the right ventricular pressure is usually found to be less than 40 mm./Hg.¹³⁸ Compensatory infundibular hypertrophy may cause some temporary residual gradient in this area, but as the thickness of the ventricular myocardium in the right outflow tract decreases following the release of the valvular stenosis, this gradient gradually disappears with time; and after two or three years, the dynamics will be found to be essentially normal. Some valvular regurgitation may be created, but it has not been found necessary to re-operate on any patients because of residual infundibular obstruction.

At the University of Colorado 69 consecutive patients have had an open repair of isolated pulmonary valvular stenosis without mortality, and 9 patients had open resection of isolated infundibular stenosis, with one death. This technique is now widely used in the United States and Europe.

2. *Atrial septal defect*.—Suture closure of the high secundum and foramen ovale defects can be easily achieved under hypothermia. Even the very large

defects do not need placement of prosthetic devices since the huge right atria provide ample wall to allow closure by continuous suture. The presence of aberrant pulmonary venous drainage occurs in about 15% of patients, but operative techniques to overcome this additional anomaly have been described by both Lewis et al.¹³⁹ and Swan et al.^{104,140} Great care must be taken to avoid the inadvertent transplation of the inferior cava to the left auricle, and the air must be thoroughly evacuated from the left ventricle before the final stitch is taken to avoid air embolism. If more than six minutes is required for the procedure, multiple circulatory occlusions permit adequate intracardiac time. Accurate preoperative diagnosis, of course, is essential since it is undesirable for the surgeon to be operating with hypothermia alone and then find the lesion to be a primum type defect for which he would like to use the pump oxygenator. Such diagnostic accuracy, however, is quite possible with modern cardiological evaluation.¹⁴¹

In the early development of the technique, Swan et al.,¹³ operated upon 43 patients with 7 deaths. Subsequently, 137 additional patients were repaired with only 3 deaths. It would seem, therefore, that the current risk of this technic is somewhat less than two per cent. Derra,¹⁴² Brom,¹⁰⁶ and Bedford et al.¹⁴³ have continued to use this method with excellent results.

3. *Trilogy of Fallot*.—Since the Trilogy of Fallot consists essentially of the combination of valvular pulmonic stenosis and a foramen ovale septal defect, it was one of the earliest of the cyanotic forms of congenital heart disease to be attacked surgically with open technique. At first it was thought that relief of the pulmonic stenosis alone might prove to be adequate treatment if the post-operative fall in right ventricular pressure resulted in a significant decrease in the right-to-left shunt through the atrial septal defect. Indeed, this result does occur in many patients. An occasional such patient may need a second-stage closure of the septal defect. Since, however, both defects can be completely corrected at a single operation using multiple circulatory occlusions at low risk, Swan et al.,¹⁴⁴ after experience with 23 surgical patients, recommend the single stage curative procedure.

4. *Aortic stenosis*.—Although by 1954 the open attack on the pulmonary valve had become commonplace, surgeons hesitated to use the same approach to the aortic valve for fear of air embolism to the coronary or cerebral circulations. Experimental observations in dogs indicated that, even though the coronary ostia were exposed to the room air, there was not a tendency for air embolism to the coronary or cerebral circulations. Accordingly, Swan and Kortz¹⁴⁵ reported the first successful open operation on the aortic valve in man using inflow occlusion during hypothermia. Soon afterwards, Lewis et al.¹⁴⁶ successfully employed an almost identical technic in one of two patients. Subsequently, of course, with the development of successful pump-oxygenators, most aortic valvular surgery has been done during total extracorporeal bypass. The use of hypothermia alone, however, for congenital stenosis of the aortic valve and for early acquired valvular disease has continued to have supporters.¹⁴⁷ The congenitally fused, often bicuspid aortic valve can be carefully and accurately incised in the commissures within the six minute time limit. To create regurgitation of the aortic valve is disastrous; therefore, these incisions

must be made precisely, leaving intact competent cusps. The occasional patient with infundibular aortic stenosis is better operated upon during total body perfusion.

The addition of a constant perfusion of blood into the coronary circulation from a blood reservoir was studied and then attempted clinically by Shumway et al.,⁷⁴ Spencer et al.,¹⁴⁸ and Maloney et al.¹⁴⁹ No great extension in permissible occlusion time was obtained, the mortality and morbidity rates paralleled those patients not receiving perfusion, and the technic had the disadvantage of increasing the blood in the operative field. For these reasons, the method did not receive wide acceptance. However, the use of this technic during cardiac arrest and extracorporeal circulation is of distinct value and is described below.

The current experience at the University of Colorado includes open operation during hypothermia on 23 patients with congenital valvular disease, with 2 deaths. In addition, 5 patients with acquired stenosis were repaired with 0 deaths. The degree of improvement in the former group was excellent, while in the latter, fair. Extensive calcific aortic stenosis remains a challenging problem to the cardiac surgeon.

5. *Other defects.*—Other rare lesions capable of open repair during hypothermia alone include aortico-pulmonary fistula, sinus of Valsalva fistula, coronary arterial fistula to right ventricle, and aberrant pulmonary venous drainage.

B. *As an Adjunct for Closed Heart or other Thoracic Surgery*

Bigelow¹⁰⁵ was the first to urge the use of hypothermia as an adjunct in the surgery for far advanced mitral disease with cardiac failure, and successfully treated obviously high-risk patients who had massive cardiac dilatation. After relief of their mitral obstruction, they were much improved clinically and their heart size reduced remarkably. At the University of Colorado, we have had similar experiences with 8 mitral patients. The hypothermia reduces the heart rate, cardiac output and work load of the heart and minimizes the dose of narcotic agents necessary because of its anesthetic action. In addition, a safety factor is provided and if desirable for any reason the circulation can be safely arrested for 6 to 8 minutes. For these reasons, we have chosen to use hypothermia for patients with large patent ductus, aortico-pulmonary fistula, total anomalous venous drainage, tricuspid atresia, tetralogy, and transposition.

For similar reason, hypothermia has been urged for patients undergoing surgery for a wide variety of diseases in general and thoracic surgery. Brewer and King¹⁵⁰ emphasized its use in the aged and debilitated, and Eiseman et al.¹⁵¹ and Reeves and Lewis,¹⁵² for various general surgical conditions, particularly cirrhosis of the liver.

C. *As an Adjunct for Surgery of the Aorta*

The experimental studies indicating that moderate hypothermia markedly prolongs the period during which the descending aorta may be clamped without damage to the cord or to the kidneys have been described. This beneficial effect has been used clinically by a number of surgeons to permit the prolonged

clamping necessary for the resection of coarctation or aneurysms of the descending aorta. Thus, Julian et al.¹⁵³ described this clinical application in 2 patients with aneurysm and 6 with coarctation. DeBakey, et al.¹⁵⁴ and Gwathmey et al.¹⁵⁵ have had extensive satisfactory experience with this technique. At the University of Colorado in 1947, a patient suffered paraplegia following resection of coarctation. Since 1954, therefore, all adult patients with coarctation have been cooled as a protective measure against cord damage. To date, in 20 patients so treated, neurologic injury has not occurred.

THE COMBINED USE OF HYPOTHERMIA AND EXTRACORPOREAL CIRCULATION

The obvious factor limiting the use of hypothermia alone is the time available for the performance of intracardiac repair and reconstruction. Complicated and difficult lesions need considerable time for their repair, and therefore the use of a pump-oxygenator is mandatory in repairing such defects. However, distinct advantages are to be obtained from the combination of extracorporeal circulation and hypothermia.

1. *Safety Factors*

A cold heart is better able to withstand anoxia than a warm one, and therefore a safety margin exists in the event of any unforeseen mishap during the perfusion. Also the heart rate is slowed by the hypothermia, and if cardiac arrest is not desired, at least the surgeon has the benefit of working with a slowly beating heart. If, however, the heart does stop, the greatly reduced metabolic demands of the cold heart enable a longer permissible time before the return of adequate circulation without subsequent difficulty. Additional protection is also afforded to the brain.

2. *Reduced Oxygen Requirement*

The extent of the reduction in oxygen requirement depends upon the degree of hypothermia but permits the use of a smaller oxygenator with a lower blood flow and consequently less trauma to the blood. The decrease in the amount of blood required is also a definite consideration in view of the increasing number of open-heart operations being done.

3. *Change in Diagnosis*

If the patient is first cooled in the tub and subsequently attached to the pump-oxygenator, it is possible, on occasion, to dispense with the pump-oxygenator, if it is found that the diagnosis is such that the operation could be done adequately with hypothermia alone. The patient need not then be exposed to hazards both known and unknown of perfusion.

4. *Technical Advantages*

It is possible to stop the perfusion completely in a cooled patient for some minutes if the situation should demand a completely dry, bloodless field. With the patient's temperature at 30 C. the perfusion can be stopped for at least five minutes without any fear of cerebral damage, and this maneuver can give valuable assistance to the surgeon. This procedure may be repeated several times during a long perfusion if necessary, but care should be taken to see

that the electroencephalogram returns to normal between each period of circulatory arrest.

The combination of hypothermia with extracorporeal circulation does not necessarily complicate the perfusion technique. The hypothermia can be induced by one of three methods. Either the patient is cooled in an ice-water tub prior to the operation in which case only moderate hypothermia down to 30 C. can be used, or a heat-exchanger is incorporated into the circuit¹⁵⁷ and after the patient is cannulated for the perfusion is cooled by being perfused with cold blood. The first technic has the disadvantage of being somewhat slow in large adult patients and limited in the degree of hypothermia obtainable. However, it has the advantage of producing a uniform degree of hypothermia without temperature gradients between various tissues and organs, and this may well be advantageous in preventing the perfusion of relatively warm tissues by very cold blood, with a resultant relative hypoxia. Most of the heat exchangers available are variations of the one introduced by Brown,¹²² and combine the properties of efficiency with ease of sterilization. Naturally they present some resistance to the flow of blood but if a double heat exchanger has to be used in a large patient, this resistance can be greatly reduced by placing the exchangers in parallel rather than in series. If a heat exchanger is used, the advantages outlined above of being able to change the operation from one using a pump-oxygenator to one with hypothermia alone are not obtainable, because the patient has to be cannulated in order to be cooled. The third method for the induction of deep hypothermia as described by Drew,¹²⁶ Shields and Lewis,¹²⁷ is detailed below.

In general, the use of a heat exchanger has become the more acceptable technic because of the rapidity with which hypothermia can be induced, and because of the ease with which the patient can be rewarmed at the end of the procedure. The induction of hypothermia in this manner results in definite differences in temperature between various tissues of the body. The muscle cools the least and the rectal temperature is usually the lowest. Brain and esophageal temperatures are intermediate but the temperature of the brain may be several degrees higher than that of the esophagus. During the perfusion the esophageal temperature should be taken as the guide to the temperature of the heart.

In many centers the combined use of hypothermia and extracorporeal circulation has become almost routine although the degree of hypothermia used is variable.

THE USE OF DEEP HYPOTHERMIA FOR OPEN-HEART SURGERY

In 1954 Gollan²⁷ was the first to reduce the temperature of a dog to 0 C. using an extracorporeal circuit. The circulation of the animal was stopped completely and the animal recovered.

Deep hypothermia may be induced by the use of a standard system of total cardiopulmonary bypass including a heat exchanger,¹⁵⁷ or using the patient's own lungs as an autogenous oxygenator with separate circuits for the pulmonic and systemic circulations. The main advantage of using deep hypothermia is the extremely dry motionless surgical field which can be obtained at temperatures around 15 C. with total cessation of circulation and respiration for periods

of 45–60 minutes. It appears that cessation of the circulation for 45 minutes is safe in the human, at temperatures not higher than 15 C. Even at these temperatures there is consumption of oxygen,²² and it may be advantageous to maintain the circulation with the pump-oxygenator rather than obtain complete cessation of circulation.

The advantages of using deep hypothermia are:

- 1) There is maximal protection for the heart during periods of anoxia and/or cardiac arrest.
- 2) It is possible to have a prolonged period of total arrest of circulation and respiration with an extremely dry and motionless surgical field.
- 3) If the Drew technique is used the quantity of blood necessary to prime the circuit is only 1,200 to 1,500 cc., and the absence of an oxygenator results in diminished trauma to the blood.

However, the method is not without disadvantages. If the patient's lungs are diseased then their efficiency as an oxygenator may be impaired. Thus it is probably inadvisable to use this technique in patients with pulmonary hypertension and possible pulmonary vascular changes. In the experimental animal pulmonary edema is not uncommon although the pulmonary artery pressure during the perfusion may not exceed 20–25 mm./Hg at the time the pulmonary edema develops. Cerebral damage has been noted by Bjork⁸¹ and the same type of damage has also been experienced by other surgeons using this technic. As mentioned above, it may be due to intravascular aggregation of platelets and white cells resulting in micro-infarcts.

Several hundreds of patients have now been operated on using this technique in Europe, England, and the United States. Many of these patients have been severe risks and therefore inevitably the mortality rate has been high, but not excessively so. A wide variety of lesions has been attacked and the technic has particular merit in those operations where detailed, meticulous suturing is required under entirely motionless, bloodless conditions, such as for the repair and reconstruction of aortic valves.¹⁵⁸

THE USE OF HYPOTHERMIA FOR THE INDUCTION OF CARDIAC ARREST

Credit must go to Melrose¹⁵⁹ for introducing the concept of induced cardiac arrest using potassium citrate perfusion of the coronary arteries. This method demonstrated that the heart could be stopped, operated upon, and restarted again. However, it has since been shown that potassium damages the myocardium.¹⁶⁰ Focal necrosis and fibrosis may result with the development of heart failure some weeks or months postoperatively. Moreover, the ability of the heart to perform work immediately after the period of cardiac arrest is seriously impaired.¹⁶¹ Other pharmacologic methods of inducing cardiac arrest similarly reduce the ability of the ventricles to perform work in the immediate post-operative phase. However, the induction of cardiac arrest by hypothermia while still diminishing the heart's capabilities does not result in such a serious deterioration in cardiac function. Therefore, cold arrest of the heart is probably the technic of choice at the present time.

The temperature of the heart has to be reduced to about 15–17 C. before it will stop. This can be done by perfusion of the coronary arteries with cold

blood from the pump-oxygenator, by perfusion of the coronaries with cold oxygenated blood from a separate circuit, or by surrounding the heart with frozen Ringer's solution, and the rapid induction of local deep hypothermia. At the same time, the coronary arteries may be perfused by a mixture of cold blood and Ringer's solution so that cooling of the myocardium does not depend entirely upon heat loss at the epicardial surface. In spite of the protection afforded to the myocardium by cold arrest, it is probably advisable to maintain some perfusion of the coronary arteries while the heart is arrested. This is particularly true in large hypertrophied hearts such as are found in severe aortic valvular disease. These hearts because of their large muscle mass are peculiarly susceptible to periods of anoxia and have, in addition, a significant reluctance to restart after a period of arrest. Thus it is essential that they should be afforded every protection during the period of arrest, and such protection is probably best afforded by cannulation and perfusion of the coronary arteries with 200–350 cc. of blood per minute during the period of arrest. At the same time, it is most important that none of the chambers of the heart should be allowed to dilate and, therefore, appropriate cannulae should be inserted into the left and right sides of the heart at the start of the procedure while the heart is still beating so that under no circumstances will dilatation of the heart occur while it is arrested. Even momentary dilatation of a ventricle may result in irreparable damage, inability to restart, and the death of the patient.

CONCLUSIONS

Within the short space of eleven years the technic of hypothermia has evolved from an exciting, but tentative, concept into a widely accepted, useful, and safe modality. Its uses have neither been exhausted nor fully explored.

In the field of cardiovascular surgery the use of hypothermia alone without the additional use of extracorporeal circulation is a satisfactory method for the surgical therapy of secundum atrial septal defects, Trilogly of Fallot, isolated pulmonary stenosis both valvular and infundibular, congenital aortic stenosis and aortopulmonary window. It is a valuable adjunct to major cardiovascular surgery of other types and this aspect of its use deserves wider attention.

The induction of moderate hypothermia requires only equipment available in almost any hospital and is, therefore, readily applicable on a widespread basis. The inclusion of an extracorporeal circuit with its complexities—mechanical, electronic and administrative—widens the surgical scope of procedures possible, but narrows the topographical applicability to larger centers with substantial financial underwriting, good blood banking facilities and extensive staff. Therefore, it would seem that the smaller centers should be encouraged to develop the simpler technics of moderate hypothermia. However, no center should embark on this type of surgery unless adequate diagnostic facilities are readily available. A period of total inflow occlusion is not the time to make the diagnosis. Moderate hypothermia appears to offer definite advantages in many circumstances when combined with extracorporeal circulation.

The potentialities of deep hypothermia have not yet been fully evaluated.

It appears that patients can be cooled to 10–15 C. and subjected to complete cessation of respiration and circulation for prolonged periods with an acceptable mortality. However, the mere ability to refrigerate patients does not, by itself, justify the use of this method unless it can be shown that distinct advantages accrue from this modality which are unobtainable by other means. Such advantages as the immobility and bloodlessness of the operative field are already apparent and, for this reason alone, deep hypothermia already has a place in the cardiac surgeon's armamentarium.

REFERENCES

1. Talbott, J. H.: Physiologic and therapeutic effects of hypothermia. *New England J. Med.* 224:281, 1941.
2. Swan, H.: The current status of hypothermia. *A.M.A. Arch. Surg.* 69:597, 1954.
3. Collan, F.: Cardiac arrest of one hour duration in dogs during hypothermia of 0° C. followed by survival. *Fed. Proc.* 13:57, 1954.
4. Niazi, S. A., and Lewis, F. J.: Resumption of heart beat in dogs after standstill at low temperatures. *Surg. Forum* 5:113, 1954.
5. Smith, A. U.: Viability of supercooled and frozen mammals. *Ann. New York Acad. Sc.* 80:291–300, 1959.
6. Adams, F.: *The Genuine Works of Hippocrates*. New York, William Woods and Co., 1886.
7. Currie, J.: *Medical Reports on the Effects of Water, Cold, and Warm, as a Remedy in Fever and Other Diseases, Whether Applied to the Surface of the Body or Used Internally*. Liverpool, England, First Edition, 1797.
8. Hunter, J.: Experiments and observations on animals, with respect to the power of producing heat. *In Observations on Certain Parts of the Animal Oeconomy*. London, 1786.
9. Walther, A.: *Beitrag zur Lehre von Thierschen Warme*. *Virchows Arch. F. Path. Anat.* 25:414, 1862.
10. Smith, L. W., and Fay, T.: Observations on human beings with cancer maintained at reduced temperatures of 75–90 F. *Am. J. Clin. Path.* 10:1, 1940.
11. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General hypothermia for experimental intracardiac surgery. *Ann. Surg.* 132:531, 1950.
12. Lewis, F. J., and Taufic, M.: Closure of atrial septal defects with aid of hypothermia. Experimental accomplishments and report of one successful case. *Surgery* 33:52, 1953.
13. Swan, H., Zeavin, I., Blount, S. G., Jr., and Virtue, R. W.: Surgery by direct vision in the open heart during hypothermia. *J.A.M.A.* 153:1081, 1953.
14. Niazi, S. A., and Lewis, F. J.: Tolerance of adult rats to profound hypothermia and simultaneous cardiac standstill. *Surgery* 36:25, 1954.
15. Simpson, S.: Temperature range in the monkey in ether anesthesia. *J. Physiol., London* 28:38, 1902.
16. Lowenhardt, D.: Ueber Eine Form Von Manie Mit Tiefer Temperatur-Senkung. *Allg. Ztschr. f. Psychiat.* 25:685, 1868.
17. Alexander, L.: The treatment of shock from prolonged exposure to cold, especially in water. *London Combined Intell. Object. Subcom.* 1945 (Forms file No. XXVI-37, Item No. 24, CIOS report, London).
18. Laufman, H.: Profound accidental hypothermia. *J.A.M.A.* 147:1201, 1951.
19. Dill, D. B., and Forbes, W. H.: Respiratory and metabolic effects of hypothermia. *Am. J. Physiol.* 132:685, 1941.
20. Adolph, E. F.: Oxygen consumptions of hypothermic rats and acclimatization to cold. *Am. J. Physiol.* 161:359, 1950.
21. Hegnauer, A. H., and D'Amato, H.: Oxygen consumption and cardiac output in the hypothermic dog. *Am. J. Physiol.* 178:138, 1954.
22. Gordon, A. S., Jones, J. C., Luddington, L. G., and Meyer, B. W.: Deep hypothermia for intracardiac surgery:

- experimental and clinical use without an oxygenator. *Am. J. Surg.* 100: 332, 1960.
23. Kameya, S., Oz, M., Neville, W. E., and Clowes, G. H. A.: A study of oxygen consumption during profound hypothermia induced by perfusion of the entire body. *Surg. Forum* 11: 190, 1960.
 24. Brown, W., and Hill, A. V.: The oxygen dissociation curve of blood and its thermo-dynamical basis. *Proc. Roy. Soc. London, B.* 94:297, 1923.
 25. Rosenhain, F. R., Penrod, K. E., and Flynn, J.: Blood gas studies in the hypothermic dog. *Am. J. Physiol.* 166:55, 1951.
 26. Edwards, W. S., Simmons, E., Lombardo, C. R., Bennett, A., and Bing, R. J.: Coronary blood flow in hypothermia. *A.M.A. Arch. Surg.* 71:853, 1955.
 27. Gollan, F., Hoffman, J. E., and Jones, R. M.: Maintenance of life of dogs below 10 C. without hemoglobin. *Am. J. Physiol.* 179:640, 1954.
 28. Rosenthal, T. B.: Effect of temperature on the pH of blood and plasma in vitro. *J. Biol. Chem.* 173:25, 1948.
 29. Trede, M., Foote, A. V., and Maloney, J. V., Jr.: Pathophysiologic aspects of deep hypothermia with extracorporeal circulation. In press.
 30. Brewin, E. G., Gould, R. P., Nashat, F. S., and Neil, E.: An investigation of problems of acid base equilibrium in hypothermia. *Guy's Hosp. Reports* 104:177, 1955.
 31. Waddell, W. G., Fairley, H. B., and Bigelow, W. G.: Improved management of clinical hypothermia. *Ann. Surg.* 146:542, 1957.
 32. Fairley, H. B., Waddell, W. G., and Bigelow, W. G.: Hypothermia for cardiovascular surgery. Acidosis in the rewarming period. *Brit. J. Anaesth.* 29:310, 1957.
 33. Gordon, A. S., Meyer, B. W., and Jones, J. C.: Open heart surgery using deep hypothermia without an oxygenator. *J. Thorac. & Cardiovasc. Surg.* 40:787, 1960.
 34. Ballinger, W. F., Volleweider, H., Templeton, J. Y., Pierucci, L.: The acidosis of hypothermia. *Am. Surgical Assoc., Florida*, 1961.
 35. Hegnauer, A. H., Shriber, W. J., and Haterius, H. V.: Cardiovascular response of the dog to immersion hypothermia. *Am. J. Physiol.* 161:455, 1950.
 36. Penrod, K. E., and Flynn, J.: Cardiac oxygenation during severe hypothermia in dogs. *Am. J. Physiol.* 164: 79, 1951.
 37. D'Amato, H. E., and Hegnauer, A. H.: Blood volume in the hypothermic dog. *Am. J. Physiol.* 173:100, 1953.
 38. Fisher, B., Russ, C., Fedor, E., Wilde, R., Engstrom, P., Happel, J., and Prendergast, P.: Experimental evaluation of prolonged hypothermia. *A.M.A. Arch. Surg.* 71:431, 1955.
 39. Wynn, V.: Electrolyte disturbances associated with failure to metabolise glucose during hypothermia. *Lancet*, 2:575, 1954.
 40. Elliott, H. W., and Crismon, J. M.: Increased sensitivity of hypothermic rats to injected potassium and the influence of calcium, digitalis and glucose on survival. *Am. J. Physiol.* 151: 366, 1947.
 41. McMillan, I. K. R., Melrose, D. G., Churchill-Davidson, H. C., and Lynn, R. G.: Hypothermia: some observations on blood gas and electrolyte changes during surface cooling. *Ann. Roy. Coll. Surg. England* 16:186, 1955.
 42. Fabian, L. W., Stainton, R., Harra, M., Ling, P. C., and Shafer, C. W.: Chemophysiologic alterations during hypothermia, ganglioplegia and intracardiac surgery. *Anesthesia & Analgesia* 34:214, 1955.
 43. Fleming, R.: Acid base balance of the blood in dogs at reduced body temperature. *A.M.A. Arch. Surg.* 68: 145, 1954.
 44. Hamilton, J. B., Dresbach, M., and Hamilton, R. S.: Cardiac changes during progressive hypothermia. *Am. J. Physiol.* 118:71, 1937.
 45. Blair, E., Austin, R. R., Blount, S. Gilbert, Jr., and Swan, H.: A study of the cardiovascular changes during cooling and rewarming in human subjects undergoing total circulatory occlusion. *J. Thorac. Surg.* 33:707,

- 1957.
46. Lofstrom, B.: Induced hypothermia and intravascular aggregation. *Acta. Anaest. Scand. Supp.* 3:1-19, 1959.
 47. Gelin, L. E., and Lofstrom, B.: A preliminary study on peripheral circulation during deep hypothermia. *Acta. Chir. Scandinav.* 108:402, 1955.
 48. Long, D. M., Sanchez, L., Varco, R. L., and Lillehei, C. W.: Use of plasma expanders in extracorporeal circulation. *Soc. of Univ. Surgeons, Kansas City*, 1961.
 49. Fuhrman, G. J., Fuhrman, F. A., and Field, J.: Metabolism of rat heart slices with special reference to effects of temperature and anoxia. *Am. J. Physiol.* 163:642, 1950.
 50. Berne, R. M.: The effect of immersion hypothermia on coronary blood flow. *Circul. Res.* 2:237, 1954.
 51. Berne, R. M.: Myocardial function in severe hypothermia. *Circul. Res.* 2: 90, 1954.
 52. Hicks, C. E., McCord, M. C., and Blount, S. G., Jr.: Electrocardiographic changes associated with hypothermia and circulatory occlusion. *Clin. Res. Proc.* III, 2:107, 1955.
 53. Osborn, J. J.: Experimental hypothermia: respiration and blood pH changes in relation to cardiac function. *Am. J. Physiol.* 175:389, 1953.
 54. Emslie-Smith, D., Sladden, G. E., and Stirling, G. R.: The significance of changes in the electrocardiogram in hypothermia. *Brit. Heart. J.* 21:343, 1959.
 55. Kirby, C. K., Jensen, J. M., and Johnson, J.: Defibrillation of the ventricles under hypothermic conditions. *A.M.A. Arch. Surg.* 68:663, 1954.
 56. Hegnauer, A. H., and Angelakos, E. T.: Excitable properties of the hypothermic heart. *Ann. New York Acad. Sc.* 80:336, 1959.
 57. Edwards, W. S., Simmons, E., Lombardo, C. R., Bennett, A., and Bing, R. J.: Coronary blood flow in hypothermia. *A.M.A. Arch. Surg.* 71:853, 1955.
 58. Swan, H.: Hypothermia for general and cardiac surgery, with techniques of some open intracardiac procedures under hypothermia. *Surg. Clin. N. Amer.* 36:1, 1956.
 59. Montgomery, V., Prevedel, A. E., and Swan, H.: Prostagmine inhibition of ventricular fibrillation in the hypothermic dog. *Circulation* 10:721, 1954.
 60. Covino, B. G., Charleson, D. A., and D'Amato, H. E.: Ventricular fibrillation in the hypothermic dog. *Am. J. Physiol.* 178:148, 1954.
 61. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V.: Cessation of circulation in general hypothermia. I. Physiologic changes and their control. *Ann. Surg.* 138:360, 1953.
 62. Niazi, S., and Lewis, F. J.: The effect of carbon dioxide on heart block and ventricular fibrillation during hypothermia in rats and dogs. *Surg. Forum* 5:106, 1954.
 63. Shumacker, H. B., Riberi, A., Boone, R. D., and Kajikuri, H.: Ventricular fibrillation in the hypothermic State. IV. The role of extrinsic cardiac innervation. *Ann. Surg.* 143:223, 1956.
 64. Navratil, J.: Prevention and treatment of ventricular fibrillation. *Am. Surgeon* 22:436, 1956.
 65. Hegnauer, A. H., D'Amato, H.: Oxygen consumption and cardiac output in the hypothermic dog. *Am. J. Physiol.* 178:138, 1954.
 66. Brown, T. G., and Cotten, M. V.: Evaluation of factors enhancing cardiac force during hypothermia. *Fed. Proc.* 15:405, 1956.
 67. Steinhaus, J. E., Siebecker, K. L., and Kimmey, J. R.: Comparative effect of anesthetic agents on cardiac irritability during hypothermia. *J.A.M.A.* 169:8, 1959.
 68. Gollan, F., Tysinger, D. S., Grace, J. T., Kory, R. C., and Meneely, G. R.: Hypothermia of 1.5° C. in dogs followed by survival. *Am. J. Physiol.* 181:297, 1955.
 69. Berman, E. J., Taylor, M. T., Fisch, C.: Experimental prevention of ventricular fibrillation following hypothermia and induced cardiac arrest. *J. Thorac. Surg.* 35:483, 1958.
 70. Angelakos, E. T.: Influence of pharmacological agents on sponta-

- neous and surgically induced hypothermic ventricular fibrillation. *Ann. New York Acad. Sc.* 80:351, 1959.
71. Johnson, P., LeSage, A., Floyd, M. D., Young, W. G., and Sealy, W. C.: Prevention of ventricular fibrillation during profound hypothermia by quinidine. *Ann. Surg.* 151:490, 1960.
 72. Niazi, S., and Lewis, F. J.: The effect of carbon dioxide on heart block and ventricular fibrillation during hypothermia in rats and dogs. *Surg. Forum* 5:106, 1954.
 73. Caranna, L. J., Telmosse, J. P., and Swan, H.: Effect of intravenous nutrient solutions on ventricular fibrillation in the hypothermic dog. *A.M. A. Arch. Surg.* 76:394, 1958.
 74. Shumway, N. E., Gliedman, H. L., and Lewis, F. J.: Coronary perfusion for longer periods of cardiac occlusion under hypothermia. *J. Thorac. Surg.* 30:598, 1955.
 75. Riberi, A., Siderys, H., and Shumacker, H. B., Jr.: Ventricular fibrillation in the hypothermic state. I. Prevention by sino-auricular node blockade. *Ann. Surg.* 143:216, 1956.
 76. Parkins, W. M., Jensen, J. M., and Vars, H. M.: Brain cooling in the prevention of brain damage during periods of circulatory occlusion in dogs. *Ann. Surg.* 140:284, 1954.
 77. Adams, J. E., and Pevehouse, B. C.: Regional hypothermia of the brain. *Clin. Neurosurg.* 6:104-18, 1958.
 78. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in the dog. *Surg. Gyn. & Obst.* 102:98, 1956.
 79. Sano, M. E., and Smith, L. W.: Critical histopathological study of fifty post-mortem patients with cancer subjected to local or generalized refrigeration compared to a similar control group of thirty-seven non-refrigerated patients. *J. Lab. & Clin. Med.* 26: 443, 1940.
 80. Stephens, J., and Appleby, S.: Polyneuropathy following induced hypothermia. *Tr. Am. Neurol. Assoc.* 80: 102, 1955.
 81. Bjork, V. O.: An effective blood heat exchanger for deep hypothermia in association with extracorporeal circulation but excluding the oxygenator. *J. Thorac. & Cardiovasc. Surg.* 40:237, 1960.
 82. Denny-Brown, D., Adams, R. D., Brenner, C., and Doherty, M. M.: The pathology of injury to nerve induced by cold. *J. Neuropath. and Exper. Neurol.* 4:305, 1945.
 83. Virtue, Robert W.: *Hypothermic Anesthesia.* Springfield, Ill., Charles C Thomas, 1955.
 84. Scott, J. W.: The E. E. G. during hypothermia. *E. E. G. Clin. Neurophysiol.* 7:466, 1955.
 85. Fazekas, J. F., and Himwich, H. E.: Effect of hypothermia on cerebral metabolism. *Proc. Soc. Exper. Biol. Med.* 42:537, 1939.
 86. Field, J., II, Fuhrman, F. A., and Martin, A. W.: Effects of temperature on the oxygen consumption of brain tissue. *J. Neurophysiol.* 7:117, 1944.
 87. Stone, H. H., Donnelly, C., and Froese, A. S.: The effects of lowered body temperature on the cerebral hemodynamics and metabolism of man. *Surg. Gyn. Obst.* 103:313, 1956.
 88. Lougheed, W. M., and Kahn, D. S.: Circumvention of anoxia during arrest of cerebral circulation for intracranial surgery. *J. Neurosurg.* 12: 226, 1955.
 89. Pontius, R. G., Bloodwell, R. O., Cooley, D. A., and DeBaKey, M. E.: The use of hypothermia in the prevention of brain damage following temporary arrest of cerebral circulation: experimental observations. *Surg. Forum*, W. B. Saunders & Co., p. 224, 1954.
 90. Owens, J. C., Prevedel, A. E., and Swan, H.: Prolonged experimental occlusion of thoracic aorta during hypothermia. *A.M.A. Arch. Surg.* 70: 95, 1955.
 91. Rosomoff, H. L., Shulman, K., Raynor, R., and Groinger, W.: Experimental brain injury and delayed hypothermia. *Surg. Gyn. Obst.* 111:27, 1960.
 92. Williams, R. G., and Spencer, F. C.: The clinical use of hypothermia following cardiac arrest. *Ann. Surg.* 148:462, 1958.
 93. Khalil, H. H.: Effects of hypothermia on the hypothalamic-pituitary re-

- sponse to stress. *Brit. M. J.* 2:733, 1954.
94. Egdahl, R. H., Nelson, D. H., and Hume, D. M.: Adrenal cortical function in hypothermia. *Surg. Gyn. and Obst.* 101:715, 1955.
 95. Swan, H., Jenkins, D., and Helmreich, M. L.: The adrenal cortical response to surgery: III. Changes in plasma and urinary corticosteroid levels during hypothermia in man. *Surgery* 42:202, 1957.
 96. Page, L., Kupsinel, H., and Adams, J.: Effect of hypothermia on renal function. *Army Med. Research Lab. Report #152*, October 22, 1954.
 97. Miles, B., and Churchill-Davidson, H.: Effect of hypothermia on the renal circulation of the dog. *Anaesthesiology* 16:230, 1955.
 98. Segar, W. E., Riley, P. A., Jr., and Barila, T. G.: Urinary composition during hypothermia. *Am. J. Physiol.* 185:528, 1956.
 99. Morales, P., Carbery, W., Morello, A., and Morales, G.: Alterations in renal function during hypothermia in man. *Ann. Surg.* 145:488, 1957.
 100. Bernhard, W. F., Cahill, G. F., Jr., and Curtis, G. W.: The rationale of surgery under hypothermia in certain patients with severe hepatocellular disease. *Ann. Surg.* 145:289, 1957.
 101. Moore, F. D.: Personal communication, 1960.
 102. Bunker, J. P., and Goldstein, R.: Coagulation during hypothermia in man. *Proc. Soc. Exper. Biol.* 97:199, 1958.
 103. Von Kaulla, K. N., and Swan, H.: Clotting deviations in man associated with open-heart surgery during hypothermia. *J. Thorac. Surg.* 36:857, 1958.
 104. Swan, H., Virtue, R., Blount, S. G., Jr., and Kircher, L. J.: Hypothermia in surgery, analysis of 100 clinical cases. *Ann. Surg.* 142:382, 1955.
 105. Bigelow, W. G.: Operation and hypothermia. *Bull. Soc. Internat. Chir.* 14:308, 1955.
 106. Brom, A. G., and Kalsbeck, H.: Die Chirurgische Behandlung der Pulmonal Stenose. *Thorax Chirurgie* 7: 229, 1957.
 107. Zindler, M.: Die Kunstliche Hypothermie in der Praktischen Chirurgie. *Arch. Klin. Chir.* 284:212, 1956.
 108. Sellick, B. A.: A method of hypothermia for open heart surgery. *Lancet* 1:443, 1957.
 109. Wilson, J. N., Marshall, S. B., Beresford, V., Montgomery, V., Jenkins, D., and Swan, H.: Experimental hemorrhage: the deleterious effect of hypothermia on survival and a comparative evaluation of plasma volume changes. *Ann. Surg.* 144:696, 1956.
 110. McQuiston, W. O.: Anaesthesia in cardiac surgery. *A.M.A. Arch. Surg.* 61:892, 1950.
 111. Lewis, F. J., Ring, D. M., and Alden, J. F.: A technique for total body cooling of the febrile, gravely ill patients. *Surgery* 40:465, 1956.
 112. Blades, B., and Pierpont, H. C.: A simple method for inducing hypothermia. *Ann. Surg.* 140:557, 1954.
 113. Eichna, L. W.: Thermal gradients during varying body temperatures. *Arch. Phys. Med.* 29:687, 1948.
 114. Vermeulen-Cranch, D. M. E., and Spierdijk, J.: A Temperature controlled cabinet operating table for safe hypothermia. *Brit. J. Anaesth.* 29:400, 1957.
 115. Boerema, I., Wildschut, A., Schmidt, W. J. H., and Broekhuysen, L.: Experimental researches into hypothermia as an aid in the surgery of the heart. *Arch. Chir. Neerl.* 3:25, 1951.
 116. Delorme, E. J.: Experimental cooling of the blood stream. *Lancet* 2:914, 1952.
 117. Gollan, F., Bloe, P., and Schuman, H.: Exclusion of the heart and lungs from circulation in the hypothermic, closed-chest dog by means of a pump-oxygenator. *J. Appl. Physiol.* 5:180, 1952.
 118. Pierce, E. C., III, and Polley, V. B.: Differential hypothermia for intracardiac surgery: preliminary report of a pump-oxygenator incorporating a heat exchanger. *A.M.A. Arch. Surg.* 67:521, 1953.
 119. Brock, R., and Ross, D. N.: Hypothermia part III: The clinical application of hypothermic techniques.

- Guy's Hosp. Rep. 104:99, 1955.
120. Dogliotti, A. M., and Ciocatto, E.: Les bases physio-pathologiques de L'hypothermie et les possibilites de l'association hypothermie-circulation extra-corporelle. *Schweiz. Med. Wehnschr.* 83:707, 1953.
 121. Young, W. G., Jr., Sealy, W. C., Brown, I. W., Jr., Smith, W. W., Callaway, H. A., Jr., and Harris, J. S.: Metabolic and physiological observations on patients undergoing extracorporeal circulation in conjunction with hypothermia. *Surgery* 46:175, 1959.
 122. Brown, I. W., Jr., Smith, W. W., Young, W. G., Jr., and Sealy, W. C.: Experimental and clinical studies of controlled hypothermia rapidly produced and corrected by a blood heat exchanger during extracorporeal circulation. *J. Thorac. Surg.* 36:497, 1958.
 123. Urschel, H. C., Jr., Greenberg, J. J., and Roth, E. J.: Rapid hypothermia: an improved extracorporeal method. *J. Thorac. & Cardiovasc. Surg.* 39:318, 1960.
 124. Osborn, J. J., Bramson, M. L., and Gerbode, F.: A rotating disc oxygenator and integral heat-exchanger of improved inherent efficiency. *J. Thorac. & Cardiovasc. Surg.* 39:427, 1960.
 125. Gebauer, P. N., Brainard, S. C., Mason, C. B., and Connor, M.: A temperature control unit for a commercial disc oxygenator. *Hawaii M. J.* 19:651, 1960.
 126. Drew, C. E., Keen, G., and Benazon, D. B.: Profound hypothermia. *Lancet* 1:745, 1959.
 127. Shields, T. W., and Lewis, F. J.: Rapid cooling and surgery at temperatures below 20° C. *Surgery* 46:164, 1959.
 128. Drew, C. E., and Anderson, I. M.: Profound hypothermia in cardiac surgery. *Lancet* 1:748, 1959.
 129. Kimoto, S., Sugie, S., and Asano, K.: Open heart surgery under direct vision with the aid of brain cooling by irrigation. *Surgery* 39:592, 1956.
 130. Brooks, B., and Duncan, G. W.: Effects of temperature on the survival of anemic tissue. *Ann. Surg.* 112:130, 1940.
 131. Bruneau, J., and Heinbecker, P.: Effects of cooling on experimentally infected tissues. *Ann. Surg.* 120:716, 1944.
 132. Eiseman, B., Malette, W. G., Wotkyns, R. S., Summers, W. B., and Tong, J. L.: Prolonged hypothermia in experimental pneumococcal peritonitis. *J. Clin. Invest.* 35:940, 1956.
 133. Fedor, E. J., Fisher, B., and Fisher, E. R.: Observation concerning bacterial defense mechanisms during hypothermia. *Surgery* 43:807, 1958.
 134. Duncan, G. W., and Blalock, A.: Shock produced by crush injury. Effects of the administration of plasma and the local application of cold. *A.M.A. Arch. Surg.* 45:183, 1942.
 135. Willman, V. L., and Hanlon, C. R.: The influence of temperature on surface bleeding. Favorable effects of local hypothermia. *Ann. Surg.* 143:660, 1956.
 136. Swan, H., and Zeavin, I.: Cessation of circulation in general hypothermia III. Techniques of intra-cardiac surgery under direct vision. *Ann. Surg.* 139:385, 1954.
 137. —, Cleveland, H. C., Mueller, H., and Blount, S. G., Jr.: Pulmonic valvular stenosis. *J. Thorac. Surg.* 28:504, 1954.
 138. Blount, S. G., Jr., Van Elk, J., Balchum, O. J., and Swan, H.: Valvular pulmonary stenosis with intact ventricular septum. *Circulation* 15:6, 1957.
 139. Lewis, F. J.: Repair of atrial septal defects during hypothermia. *Postgrad. Med.* 17:293, 1955.
 140. Swan, H., Kortz, A. B., Davies, D. H., and Blount, S. G., Jr.: Atrial septal defect, secundum, an analysis of one hundred patients undergoing open surgical repair. *J. Thorac. Surg.* 37:52, 1959.
 141. Blount, S. G., Jr.: Atrial septal defect: the diagnosis and the operative results. *Rhode Island M. J.* 39:615, 1956.
 142. Derra, E.: Experiences sur le traitement de la communication interauriculaire "a coeur ouvert" sous hypothermie (55 cas operes). *Poumon & Coeur* 12:803, 1956.
 143. Bedford, E., Sellors, T. H., Somerville,

- H., Belcher, J. R., and Besterman, E. M. M.: Atrial septal defect and its surgical treatment. *Lancet* 1:1255, 1957.
144. Swan, H., Marchioro, T., Kinnard, S., and Blount, S. G., Jr.: Trilogy of Fallot, experience with twenty-two surgical cases. *A.M.A. Arch. Surg.* 81: 291, 1960.
145. —, and Kortz, A. B.: Direct vision trans-aortic approach to the aortic valve during hypothermia. Experimental observations and reports of a successful clinical case. *Ann. Surg.* 144:205, 1956.
146. Lewis, F. J., Shumway, N. E., Niazi, S. A., and Benjamin, R. B.: Aortic valvulotomy under direct vision during hypothermia. *J. Thorac. Surg.* 32:481, 1956.
147. Linder, F.: Pathophysiologie und Indikationen der Hypothermie bei Operationen am Offenen Herzen. *Arch. Klin. Chir.* 289:188, 1958.
148. Spencer, F. C., Jude, J. R., and Bahnson, H. T.: The use of coronary perfusion and carbon dioxide regulation in intracardiac operations performed under hypothermia. *Surgery* 42:76, 1957.
149. Maloney, J. V., Jr., Marable, S., and Longmire, W. P., Jr.: Coronary perfusion as an aid to the open repair of atrial septal defects under hypothermia. *J. Thorac. Surg.* 34:580, 1957.
150. Brewer, L. A., and King, E. L.: Hypothermia in thoracic and thoraco-abdominal Surgery. *Am. J. Surg.* 96: 137, 1958.
151. Eiseman, B., Owens, J. C., and Swan, H.: Hypothermia in general surgery. *New England J. Med.* 255:750, 1956.
152. Reeves, M. M., and Lewis, J. F.: Total body cooling in critically ill febrile patients. *Surgery* 44:83, 1958.
153. Julian, O. C., Grove, W. J., Dye, W. S., Sadove, H. S., Javid, H., and Rose, R. F.: Hypotension and hypothermia in surgery of the thoracic aorta. *A.M.A. Arch. Surg.* 70:729, 1955.
154. DeBakey, M. E., Cooley, D. A., and Creech, O., Jr.: Resection of the aorta for aneurysms and occlusive disease with particular reference to the use of hypothermia: analysis of 200 cases. *Tr. Am. Coll. Cardiol.* 5: 153, 1955.
155. Gwathmey, O., Pierpont, H. C., and Blades, B.: Clinical experiences with the surgical treatment of acquired aortic vascular diseases. *Surg. Gyn. & Obst.* 107:205, 1958.
156. Swan, H., and Paton, B.: The combined use of hypothermia and extracorporeal circulation in cardiac surgery. *J. Cardiovasc. Surg.* 1:169, 1960.
157. Sealy, W. C., Young, W. G., Brown, I. W., Smith, W. W., and LeSage, A. M.: Profound hypothermia combined with extracorporeal circulation for open heart surgery. *Surgery* 48: 432-8, 1960.
158. Bjork, V. O.: Perfusion technic for surgery on the aortic valves. *Ann. Surg.* 153:173, 1961.
159. Melrose, D. G., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective cardiac arrest. *Lancet* 2:21, 1955.
160. Helmsworth, J. A., Kaplan, S., Clark, L. C., McAdams, A. J., Mathews, S. C., and Edwards, F. K.: Myocardial injury associated with asystole induced with potassium citrate. *Ann. Surg.* 149:200, 1959.
161. Braunwald, N. S., Waldhausen, J. A., Cornell, W. P., Bloodwell, R. D., and Morrow, A. G.: Left ventricular function following elective cardiac arrest. *Sc. Proc. Am. Heart A., Philadelphia*, p. 676, 1959.

Henry Swan, M.D., Clinical Professor of Surgery, University of Colorado School of Medicine, Denver, Colo.

Bruce C. Paton, M.D., Director of Halsted Laboratory for Experimental Surgery, University of Colorado School of Medicine, Denver, Colo.