HYPOTHERMIA

DAVID M. LITTLE, JR., M.D.

COLD is by no means a new therapeutic tool, for its numbing effects have been recognized throughout the ages, and occasional use has been made of this knowledge in medicine for centuries. Hippocrates, who advocated snow and ice to check hemorrhage, was aware of the analgesic nature of cold;[18] and refrigeration anesthesia was employed sporadically both during the Renaissance and subsequently, the most celebrated instance being by Napoleon's surgeon-general Baron Larrey, who noted that there was no pain during amputations performed on soldiers who had lain on the battlefield at low environmental temperatures. The use of refrigeration anesthesia was increased considerably in 1866 with the introduction of an ether spray for the purpose of producing local anesthesia by freezing tissues. This technique was later modified by the use of ethyl chloride which, because it evaporates more quickly, is more effective than ether in this form of anesthesia. The use of refrigeration anesthesia has been greatly extended in more recent times for amputations of gangrenous extremities.

The concept of total body hypothermia, as contrasted to refrigeration anesthesia, dates back to the time of the illustrious John Hunter, who attempted to freeze carp to a state of suspended animation;[18] but most early observations on hypothermia were limited to reports of survival after accidental exposure to severe cold or occasional physiological studies in laboratory animals. The deliberate application of hypothermia to clinical problems in medicine was pioneered by Temple Fay in 1940 for the treatment of malignant disease,[37,9] based on the observation that metastases were rare in the periphery of limbs where the temperature was lower. He obtained some striking examples of relief of intractable pain, and some regression of malignant growths, especially when the cold was applied locally, as in carcinoma of the cervix; but in general there was a failure to achieve reversal of the cancerous process. Talbott in 1941 also employed prolonged total body hypothermia, as a form of treatment in psychotic patients, but with little success and with two deaths from cardiac failure.[40,1] McQuiston made a significant contribution in 1948 when he advocated total body cooling during operations on children with cyanotic heart disease; but his original concept was to reduce oxygen demand more by counteracting hyperthermia than by the production of true hypothermia.[26,0] The current clinical interest in total body hypothermia stems chiefly from laboratory observations on the almost linear reduction of oxygen consumption that occurs with decrease in body temperature made in 1950 by Bigelow and his coworkers, who suggested the physiologic feasibility of complete occlusion of the circulation to the heart to permit intracardiac operation in a bloodless field.[42, 44, 45] Since that time, hypothermia has been employed extensively not only for intracardiac surgery, but also for a variety of other types of surgical procedures and as a therapeutic adjunct in the treatment of a variety of pathological conditions.

Hypothermia has been defined as a state of body temperature which is below normal in a homeothermic organism.[4,0,5] In common medical parlance today, however, the term has come to have a variety of connotations and denotations, depending largely upon the concepts of the individual employing the word. It becomes essential, therefore, in referring to total body hypothermia, to understand fully that the term may have different meanings according to both the depth and the duration of the hypothermia under discussion; and to realize further that there is no real uniformity as to these meanings. Thus, what is called "moderate" hypothermia by one laboratory worker

Accepted for publication August 21, 1959. Dr. Little is in the Department of Anesthesiology, Hartford Hospital, Hartford 15, Connecticut.

may be regarded as "deep" hypothermia by his clinical colleague. For purposes of semantics in this review, light hypothermia will be considered as a body temperature in the range 37–32 C., intermediate or moderate hypothermia in the range 32–26 C., deep hypothermia in the range 26–20 C., and profound hypothermia below 20 C. In similar fashion, acute hypothermia will be regarded as the production of the hypothermic state for but a few hours, and chronic or prolonged hypothermia as the production of the hypothermic state for a period of many hours, days, or even weeks.

Physiologic Effects

The exact nature of the physiologic effects produced by hypothermia will depend in large measure, as suggested above, on the depth and duration of the hypothermia, but will also vary according to the species, the age, the type of cooling, the rate of cooling, shivering, the presence or absence of anesthesia, the type and level of anesthesia, the mode of pulmonary ventilation, the nutritional status, and a host of other factors. The majority of laboratory studies have been conducted in the dog during moderate or deep hypothermia, but many other species and levels of body temperature have been used in addition. The extensive disparity in the recorded physiological effects of hypothermia has often been due to the variable conditions under which observations have been made, and it is necessary to exert caution in their interpretation. For example, acid-base shifts observed in dogs cooled during spontaneous respirations are not comparable to those seen in dogs cooled to the same temperature during adequate artificial ventilation. Quite obviously, even greater caution must be exerted in the translation to man of observations made in the experimental animal. Finally, it must be remembered that considerable individual variation will occur within a single species as far as the studies of any given parameter are concerned—and this applies, perhaps, particularly to man.

Initial Response. In general, it may be said that the initial response of the homeothermic organism to external cold is one that mimics intense sympathetic stimulation: shivering occurs, vasoconstriction is profound, oxygen consumption increases tremendously, the respiratory rate is accelerated, the pulse rate is raised, blood pressure is elevated, and there is significant increase in cardiac output.[45, 309, 318] Thus, the initial response to cooling is the opposite to that sought clinically, since the responses evoked early in the cooling period tend to decrease heat loss and increase endogenous heat production. These initial responses can be avoided to a great extent if sufficient anesthesia is administered to counter the defensive reactions induced by the powerful stimulus of cold; at about 28–30 C., "cold narcosis" supervenes and further anesthetic administration is unnecessary either to prevent shivering or to maintain unconsciousness.[44] However, even in the absence of anesthesia, and in spite of the fact that this stress response may actually produce a slight rise in temperature,[35] it will not prevent—although it may delay—the development of hypothermia.[419] In the horrible experiment performed by the Nazis at Dachau, prisoners were immersed in water at a temperature of 2–12 C.: there was initial violent shivering, succeeded by intense muscular rigidity; consciousness became clouded at rectal temperatures of 31 C.; and both muscular rigidity and shivering were abolished at rectal temperatures around 27 C.[10]

Metabolism. The metabolic effects of hypothermia obviously mirror the pattern of initial stimulation due to the shivering during early cooling, and unless shivering is prevented the oxygen consumption of the organism may increase initially several hundred per cent above the precooling rate.[45] However, when anesthesia is employed, or the body temperature is reduced to the point at which shivering and the defensive reactions are obtunded, there is an over-all reduction of bodily metabolism that is reflected in lowered oxygen consumption.[45, 119, 309, 318] There has been considerable debate as to whether this fall in oxygen consumption bears a linear [45, 119, 318] or exponential [206, 315] relationship to the drop in body temperature, but the important fact would seem to be that there is roughly a 6 per cent fall in oxygen consumption per degree centigrade fall in body temperature within the range of hypothermia employed clinically today.[299] Oxygen consumption of the dog, for instance, is reduced to 50 per cent of the normal at 30 C. [45] and 16 per cent of the normal at 23 C.[90]

It has been widely assumed that since arteriovenous oxygen differences are not apparent during cooling, and that since oxygen utilization rises during the rewarming period parallel to body temperature, oxygen debt is not incurred by the body in hypothermia; [4, 45] but more sophisticated biochemical analyses now suggest that this may not be the fact, since the reduction of oxygen uptake by the cell may not necessarily correspond to a reduction of oxygen requirement by the cell.[74] In any event, even if the body as a whole does not contract an oxygen debt during hypothermia, it is quite possible that individual organs may do so, at least during prolonged hypothermia at low temperatures.[150, 156]

Respiration. The effects of hypothermia upon respiration also mirror the pattern of initial stimulation followed by ultimate depression. There is, with the exception of the transient increases seen during the early cooling period,[45, 208, 318] a close and almost linear correlation between the fall in body temperature and the decrease in respiratory rate and depth.[4] At about 24 C. (in the dog) a respiratory crisis occurs, and the respiratory volume diminishes to the point of cessation.[208] Further cooling then necessitates artificial ventilation, and this is almost standard procedure in the experimental preparation at the temperature levels of moderate or deep hypothermia.[45]

Both the physiologic and anatomic respiratory deadspace are increased during hypothermia, apparently due to bronchodilatation; [371] but this appears to be the only major change in the lungs, since distribution and diffusion functions are well maintained as low as 20 C. in the dog. The oxygen dissociation curve is shifted to the left in hypothermia,[77] so that although oxygen combines easily with the blood's hemoglobin, it dissociates only at unusually low tissue pressures of oxygen: therefore, despite the reduced pulmonary ventilation during hypothermia, the respiratory volume is large in comparison to the volume of oxygen removed from the inspired air.[121] Nevertheless, analyses of arteriovenous oxygen differences indicate that the same fraction of oxygen is extracted from the blood at 18 C. as at 38 C. suggesting, as already noted, that the tissues contract no significant oxygen debt during hypothermia.[45, 190, 310, 340]

During rewarming, respiratory movements return at about 28 C. and regular respirations at about 30 C.[208]

Circulation. The effects of hypothermia upon the circulation, and particularly upon heart action, are crucial factors, inasmuch as with progressive cooling acute hypothermia eventually leads to either asystole or ventricular fibrillation. There is an early increase in heart rate,[193] associated with either visible or occult shivering, but after this initial tachycardia the pulse rate falls linearly with the decrease in body temperature.[20, 90, 99, 205] Heart rate, in the dog, is about 40 beats per minute at 25 C. and 15–30 beats per minute at 18–20 C.[4] This profound bradycardia is not influenced by either vagotomy or atropinization, and it is probable that it represents a direct effect of cold upon the sinus pacemaker.[318]

Of even more importance than the changes in heart rate are the disturbances of cardiac rhythm which occur during acute hypothermia. The electrocardiogram shows a prolongation of the P–R interval, lengthening of the QRS complex, and an increase in the duration of the Q–T interval.[45, 180, 218, 318, 376] These delays in intraventricular conduction time [72] are almost directly related to the temperature [105, 143, 318] and produce marked lengthening of both electrical and mechanical systole.[85] In addition, the ST segment may become elevated or depressed; and the T-wave may become diphasic, then deeply and bizarrely inverted as the temperature approaches 20 C.: [205] these latter electrocardiographic changes have been compared to those seen in myocardial anoxia.[242] Arrhythmias are frequent at temperatures below 28 C., and may take the form of nodal rhythm, premature ventricular contractions, auriculoventricular block, or even ventricular fibrillation.[44] Indeed, as already noted, when cooling is continued below 20 C., either ventricular fibrillation or cardiac asystole will occur;[13, 18] and the smaller the animals species, the lower will be the critical temperature for such cessation of effective cardiac activity.[5] A peculiar electrocardiographic wave has been noted which rises steeply from the S-wave [108, 145, 181] and is said to presage the onset of ventricular fibrillation,[56, 141, 158] although certainly fibrillation occurs often in the absence of this "current of injury." [161] Whether or not cessation

of effective cardiac activity occurs as a result of myocardial hypoxia remains debatable: [21, 22, 38] glycogen stores of the heart muscle are depleted during hypothermia,[215] but it has been claimed that there is no interference with the conversion of aerobic energy into useful work.[23] During rewarming, there is a return toward a normal electrocardiogram in the experimental animals, but the voltage of the QRS complex remains low, and the T-wave and ST segments are of different form from those seen prior to cooling.[44]

Even in the absence of serious arrhythmias, however, cardiac output falls quite markedly during hypothermia. There is an initial rise during the stimulatory phase of cooling, but then cardiac output falls to very low levels as the body temperature is reduced,[78, 220] being 14 per cent of the normal at 20 C.[44] and 10 per cent of the normal at 17 C.[190] The fall in cardiac output apparently is not due to decreased ventricular contractility; [104, 167] and although coronary blood flow is reduced rather markedly during hypothermia,[39, 133] it is thought to be sufficient to maintain an adequate supply of oxygen to the myocardium [220] since the reduction in cardiac work is proportionately greater than the reduction in coronary blood flow.[253] Deep hypothermia will depress the myocardium directly,[104, 167] however, and prolonged hypothermia may produce actual stagnant anoxemia.[156]

As a result of the decreased cardiac output, blood pressure generally falls in hypothermia,[218] but it may not always do so at the temperatures of moderate or light hypothermia employed clinically.[232] Usually, however, there is a rise in blood pressure during the early cooling period, followed by a gradual fall as body temperature is reduced: below 24 C. a crisis occurs, and there is a rapid onset of a severe degree of hypotension.[318] The fall in blood pressure is due chiefly to the reduction in cardiac output, inasmuch as the peripheral resistance, in both the systemic [45] and pulmonary circulations,[248] is increased, probably due to vasoconstriction in response to a direct action of cold blood on the arterial walls.[258]

Blood. The blood itself undergoes significant changes during deep hypothermia: viscosity is increased and there is a rather marked rise in the red blood cell count, the hemoglobin content, and the hematocrit,[114] probably due to a temporary loss of plasma from the circulating blood either as a result of trapping in the minute peripheral vessels [227] or actual shift of water to the tissues,[113] (since the red cell volume itself remains unchanged).[148] Conversely, there is an almost complete disappearance of platelets, white blood cells, and eosinophils during deep hypothermia [197, 417] as a result of sequestration in the liver, spleen, and possibly also in the gut and bone marrow.[407] This thrombocytopenia is associated with prolonged bleeding and clotting times at 20 C.,[101, 154, 277, 406] but these changes may not be seen at the temperatures of moderate hypothermia which are employed clinically.[139]

Milieu Interne. The biochemical changes of the body during hypothermia are extremely complex, and are particularly dependent upon the presence or absence of shivering, and the type of respiration. Spontaneous respiration becomes depressed during hypothermia, as already noted, and results in a fall in the *p*H of the blood,[121, 159] which is accentuated if shivering is allowed to occur during the early cooling period.[295] The development of such an acidosis may be of significance in the production of ventricular fibrillation,[400] but it can also have the theoretical advantages of counteracting the effect of low temperature on the oxygen dissociation curve, and of compensating for the depressant action of low temperature on the respiratory center.[110]

Changes in the electrolytes of the body are also much influenced by the type of ventilation and the occurrence of shivering. The concentration of serum sodium either does not change appreciably during hypothermia,[112, 119, 159, 400] or is decreased to a moderate extent.[295] Plasma potassium may fall [83, 295, 383, 400] or rise [138] during hypothermia, particularly if shivering occurs (as a result of the release of potassium by the breakdown of liver glycogen), but this rise may be prevented or converted to an actual decrease in serum potassium by hyperventilation.[400] Serum calcium is also increased during hypothermia,[19, 380] and in the presence of unchanged or decreased plasma potassium [140] can result in an increased calcium/potassium ratio which may be partially responsible for the enhanced myocardial sensitivity.[33] Considerable attention has been directed to the shifts in

concentrations of these cations, in view of the fact that cardiac conduction depends to a considerable degree upon the proper distribution of sodium, potassium, and calcium; but conflicting data exist on the question of whether or not significant changes in their concentrations occur in the myocardial cell.[34, 209, 282, 382] A linear increase in serum magnesium with reduction of rectal temperature has been demonstrated, but the relation of this finding to cardiac conduction is also not clear.[213]

Hyperglycemia occurs as a result of the shivering of early hypothermia,[102] but also occurs in the absence of shivering because of a failure to metabolize glucose at temperatures of 30 C. and below;[423] and this impairment of metabolism applies to both exogenous and endogenous glucose.[424] These facts have led a number of workers to employ glucose infusions with caution in patients during hypothermia.

Kidneys. There is a twofold effect of hypothermia on renal function, one an indirect effect upon glomerular filtration mediated via the cardiovascular system, and the other a direct effect upon tubular processes. As the body temperature is reduced, the progressive reduction in mean blood pressure leads to a reduction in renal blood flow[274] and in glomerular filtration rate.[279, 284, 302] The decrease in glomerular filtration rate, however, does not lead to a decrease in urine volume of comparable degree,[286] indicating that there is impairment of reabsorption in the distal tubules, probably as a direct effect of cold.[11] This depression of function in the distal tubules not only prevents the reabsorption of water, sodium, and glucose,[225, 366] but also the excretion of potassium,[204] and the production of ammonia and creatinine.[267] Both blood flow and filtration rate return to only about two-thirds of normal immediately upon rewarming, but are normal within twenty-four hours.[286]

Liver. Splanchnic blood flow has been shown to decrease progressively and in linear fashion as the body temperature falls during acute hypothermia.[152] This decrease in blood flow is accompanied by a decreased oxygen utilization and carbon dioxide production. The liver can apparently continue to utilize oxygen and avoid hepatocellular hypoxia even at a body temperature of 25 C.,[166] but there is suggestive evidence that during prolonged hypothermia at lower temperatures the liver may contract an oxygen debt.[155] Bile flow is slowed in the hypothermic liver,[63] and liver glycogen is rapidly utilized: in animals with ample stores of carbohydrate at the initiation of cooling, blood glucose is increased during the early phases of hypothermia and remains elevated.[424] Of great clinical importance is the effect of depressed hepatic metabolism on drug detoxification. The half life of morphine increases from 3.7 minutes at 37 C. to 94 minutes at 24 C., a twenty-three-fold increase in the time necessary for the liver to conjugate free morphine.[233] A similar, though less extensive, effect on the detoxification of thiopental has also been demonstrated, and may well apply to the conjugation and detoxification of other drugs. However, although liver function is quantitatively decreased during the actual phase of hypothermia, liver function appears to return to normal following rewarming.[152]

Endocrine System. The initial induction of hypothermia produces a stressor effect as indicated by a moderate activation of the adrenal cortex,[152, 396] but following the establishment of the hypothermic state there is depression of pituitary, ACTH, and adrenal cortical secretions.[41, 163, 232] Adrenal sensitivity to exogenous ACTH is likewise markedly reduced, apparently as a direct effect of lowered temperature on the adrenocortical cell.[124] There is a prompt return of adrenal activity upon rewarming, and, indeed, there may even be overactivity during recovery from hypothermia.[262]

Central Nervous System. The effects of hypothermia upon nervous tissue, and particularly upon the central nervous system as an entity, are varied. Cooling slows the speed of conduction in peripheral nerves,[87] impedes neuromuscular transmission,[89] and depresses the responses of the subcortical areas and the spinal cord.[386] However, it also results in a loss of "purity" of reflex response, so that a single stimulus, such as a muscle stretch, which evokes a pure monosynaptic response at normal temperature, elicits a reflex with a polysynaptic component: incoming impulses create central effects which "spill over" or involve other pathways not normally activated.[391] As progressive cooling continues a stage is reached at which a single afferent volley evokes multiple moto-

neuron discharges. In this phase of hyperactivity, hypothermia may aggravate epilepsy and certain other types of neural seizures. With progressive cooling, this hyperreflexia and response to light stimuli is abolished, cerebration is progressively delayed, and there is occurrence of retrograde amnesia.[147] These latter findings are in accord with electroencephalographic studies, which disclose a depression of cortical activity during cooling with little or no activity below 20 C.[63]

Of considerable clinical importance is the effect of hypothermia upon cerebral blood flow and cerebral oxygen consumption.[26] The level of systemic blood pressure appears to be the most important single factor controlling cerebral blood flow at hypothermic temperatures,[1] but cerebral vascular resistance is almost always increased and must also be a significant factor.[6] With the usual decrease in blood pressure seen during hypothermia in the dog there is a definite reduction of cerebral blood flow: between 35 and 25 C., there is a decrease in cerebral blood flow of 6.7 per cent per degree centigrade fall in body temperature, so that cerebral blood flow is about 50 per cent of its control value at a temperature of 29 C.[342, 345] Cerebral oxygen consumption falls at a similar rate during hypothermia in this temperature range,[342, 345] but only if shivering is prevented: it is not valid to assume that hypothermia will always depress cerebral metabolism, since, even at temperatures below 28 C., cerebral oxygen utilization may be increased over 100 per cent if shivering occurs, despite a decreased cerebral blood flow.[267] The decreased cerebral metabolism which generally pertains during hypothermia occurs in the face of an unchanged arteriovenous oxygen difference, suggesting that there is no hypoxic damage to cerebral tissue.[123]

Also of clinical importance is the effect of hypothermia upon both brain volume and the extracerebral space within the cranial cavity. In the dog at 25 C., there is a decrease in brain volume of 4.1 per cent and an increase in extra-cranial space (or that part of the intracranial space not occupied by the brain) of 31.8 per cent.[344] These changes are the results of both the fall in cerebral blood flow which has already been mentioned, and a fall in cerebrospinal fluid pressure, which occurs at a rate of 5.5 per cent per degree centigrade fall in body temperature.[344]

Both the parasympathetic and sympathetic divisions of the autonomic nervous system appear to be depressed during hypothermia, and quite markedly below 28 C.[53] The exact cause of this depression is not clear, but it may be related to the status of the neurohormones. Upon rewarming, the sympathetic component of the autonomic nervous system returns to normal, but there may be delay in the return of the parasympathetic component to normal activity.

Techniques

The most important of these various physiologic effects from the clinical point of view, of course, is the general reduction of body metabolism, and particularly the reduction of myocardial and cerebral metatbolism, that occurs during hypothermia. It is this reduction of metabolism that is sought clinically to permit temporary circulatory occlusion for operative interventions or to counteract the increased metabolism of certain pathological processes. The techniques employed to produce the hypothermic state, therefore, must be designed not only to effect body cooling, but to do so without evoking the neurologic and endocrinologic responses which may be produced by cold. These techniques have often employed complex equipment, but they are basically simple: they consist of, first, measures to control the protective reflexes (shivering and vasoconstriction); and, second, actually cooling the patient.

Anesthesia: The initial response of the homeothermic organism to surface cold is a combination of shivering and vasoconstriction. Shivering, which may be either visible or occult, or even take the form of a type of muscular rigidity, results both in a delay of cooling by the production of increased endogenous heat and in a number of undesirable physiological reactions, such as increased metabolism and increased cardiac output, that are quite the reverse of those intended.[127] Cooling is brought about by an increase in the temperature gradient between the body surface and the body core,[344] and is generally preceded by the most immediate response of the body to cold, vasoconstriction in the skin and subcutaneous tissues. Vasoconstriction not only de-

lays cooling, but also increases peripheral resistance and thus leads to increased energy expenditure by the organism. The anesthetic techniques employed in the production of hypothermia have relied variously upon chlorpromazine, general anesthesia itself, or curarization, to obtund shivering and vasoconstriction.

Chlorpromazine. Chlorpromazine has been shown to be the effective agent in the "lytic cocktail" employed to produce the mild hypothermia obtained by the French technique of artificial hibernation,[120, 284, 336] for it not only prevents shivering by a central action, but also produces vasodilatation.[216] Chlorpromazine has been employed extensively for the production of hypothermia, and it is still a valuable adjuvant to chronic hypothermia; the popularity of its use for the production of acute hypothermia, however, has waned considerably because the drug's prolonged action can lead to persistent vasodilatation and hypotension which are undesirable in the postoperative period.[324] Attempts to find other agents that would have shorter acting effects from amongst the group of autonomic blocking drugs have not been entirely successful.[244] Although a number of shorter acting adrenolytic or ganglionic blocking agents will produce vasodilatation, they do not share chlorpromazine's activity in the control of shivering.[126]

General Anesthesia. General anesthesia, if carried to sufficient depth, will of course both prevent shivering and produce vasodilatation.[45] Almost all of the general anesthetic agents have been employed for the production of hypothermia, and each has its own protagonists. Ether stimulates both respiratory rate and respiratory volume, and this respiratory drive has been considered desirable in overcoming the respiratory depression inherent in the hypothermic state.[179] Thiopental has been thought particularly useful for the prevention of cardiac arrhythmias [215, 320] and even ventricular fibrillation [332] during hypothermia, although systematic study has failed to reveal that the type of anesthesia *per se* is a significant factor in the incidence of ventricular fibrillation during hypothermia.[17] Fluothane, if administered to a sufficient depth of anesthesia, will both cause considerable vasodilatation and prevent shivering, and its non-flammability makes it a particularly desirable agent in the presence of electrocoagulation during neurosurgical procedures conducted under hypothermia.[46] Even nitrous oxide has been said to prevent the shivering inherent in the hypothermic technique (because of its analgesic action),[302] but sufficient vasodilatation for the induction of hypothermia with safe concentrations of nitrous oxide is unlikely without resort to supplemental measures.

Muscle Relaxants. In point of fact, the use of a single general anesthetic agent alone for the induction of hypothermia necessitates undesirably deep levels of anesthesia,[368] and the most common clinical practice at the present time is to use curarization in combination with light levels of general anesthesia. The precise muscle relaxant employed is not important since all will prevent shivering if given in sufficient dosage: some have used gallamine,[26] others succinylcholine,[79] but the majority of clinical workers have favored curare.[144, 412] Curarization with light general anesthesia, however, may not be capable of overcoming vasoconstriction and preventing hypertension, and in such instances it may be necessary to employ such hypotensive drugs as trimethaphan [9, 79] or the methonium compounds. It is worth noting, from the clinical point of view, that lowering muscle temperature increases the magnitude and the duration of action of such depolarizing neuromuscular blocking drugs as decamethonium and succinylcholine; whereas the intensity of neuromuscular blockade produced by substances such as *d*-tubocurarine, which block by competition with acetylcholine, is reduced by cooling.[427]

METHODS OF COOLING: The means by which actual cooling of the patient is accomplished can be classified into three major categories: surface cooling, body cavity cooling, and direct blood stream cooling.

Surface Cooling. Surface cooling has been the most popular of these methods to date. It may be accomplished by the simple application of ice bags,[175] a technique which is both inexpensive and readily available, but also slow, cumbersome, relatively unesthetic (when the ice bags leak, as they often do), and lacking in accurate control of the temperature level.

Cooling by immersion in cold water or ice

water is the most rapid (as the cooling agent is more evenly distributed over the body surface) and one of the most widely used of the various surface cooling techniques.[47, 403, 427] The technique consists of placing the patient in a tub partially filled with water and crushed ice, and when a sufficient degree of hypothermia has been accomplished, the patient is removed from the tub and positioned on the operating table. This disadvantage can be avoided by the use of a collapsible tube consisting of a rigid frame that can be attached to the operating room table to hold a large rubber or plastic sheet in the form of a tub; when the temperature has been lowered to the proper degree, the water can be quickly emptied and there is no need to move the patient, a maneuver that has been condemned as dangerous in the hypothermic state.[165, 188, 202]

Refrigerating mattresses or blankets, with coils to circulate fluid contained within them, permit either cooling or rewarming by regulation of the temperature of the circulating fluid.[42, 93, 213] This method therefore has more controllability of body temperature than immersion cooling, but the rate of cooling is relatively slower. A major disadvantage is the expense of the cooling units available commercially, although much of this expense can be avoided by the use of ingenuity in constructing simple homemade units.[7]

Air can also be used as a cooling medium in surface cooling, and extremely elaborate cold air chambers have been constructed which permit cooling by fanning cold air, or warming by blowing warm air, over the patient.[58, 160, 257, 405] Considerable controllability of body temperature has been possible with such equipment: a thermocouple adjusted to the desired rectal temperature is inserted in the rectum, and when this automatically-controlled thermocouple is activated, the rectal temperature can be held at very constant levels for hours, or even days, at a time. The disadvantages of air cooling, however, have been that the apparatus is cumbersome, since it must be a chamber of sufficient size to contain not only the patient but also the heating and cooling units and the fans, and the commercial units available are almost prohibitively expensive. A simple and inexpensive method of air cooling consists merely of spraying the surface of the body with cold tap water while fans blow upon the skin: [281] the simplicity and inexpensiveness of this method of air cooling are perhaps offset by the loss of controllability of body temperature and the rapid rate of cooling available in the cold air chamber.

Body Cavity Cooling. Body cavity cooling is a well-known technique in medicine, for cold colonic irrigations have been used by generations of physicians to counteract hyperthermia; but it has been used by only a handful of enthusiasts to induce total body hypothermia. Hypothermia can be induced during thoracotomy by perfusing cold saline into the pleural cavity, and rewarming is effected in a similar manner with warm saline.[49] The method is slow, however, since as much as 75 liters of saline may be required.[312] An additional major disadvantage is that during cooling, the heart is exposed directly to the cold solution and cardiac irregularities are common. Peritoneal perfusion has also been employed on an experimental basis, iced saline being introduced directly into the abdominal cavity to cool the blood not only as it flows through the great vessels, but also as it flows through the portal vascular bed and other abdominal viscera. The method permits direct cooling of the intestines, liver, and other abdominal viscera; but the problems of infection and the initiation of abdominal adhesions remain unresolved. The method shares the disadvantages inherent in pleural cavity cooling of being slow, cumbersome, and producing tissue temperature gradients. In intragastric cooling a balloon introduced through the esophagus into the stomach is inflated via a double-lumened connecting tube with up to 600 ml. of water at 4–6 C., and the water is then circulated back through the connecting tube by a pump to a cooling coil before being recirculated into the gastric balloon; rewarming is effected in a similar manner.[27, 233, 234] The technique is slow, but when combined with the use of a refrigerating blanket, intragastric cooling speeds the induction of hypothermia in comparison with the use of the cooling blanket alone.[203] Even the bladder, perhaps the most unlikely of the body cavities for the purpose, can be employed to produce total body hypothermia: bladder irrigations performed with fluids at room temperature will reduce the body temperature of

a small dog as much as 4.5 degrees C. per hour.[335]

Direct Blood Stream Cooling. Direct blood stream cooling, or pervascular cooling, consists of removing blood from a cannulated major vessel, cooling the blood, and then returning the blood to the body through another cannulated vessel. Arteriovenous cooling employs an artery (femoral) for the withdrawal of blood, then circulates the blood through a series of coils immersed in ice water or other refrigerant fluid, and returns the blood to a vein (femoral).[118, 347] Arteriovenous cooling has several inherent disadvantages in comparison with other methods of direct blood stream cooling: it requires cannulation of a major artery, which has been responsible for thrombosis; its efficiency decreases *pari-passu* with the development of hypothermia, since cardiac output falls and circulation of blood through the extracorporeal coil slows; and it has the effect of an arteriovenous fistula, which may accentuate or precipitate a right-to-left shunt in some patients with congenital heart disease. Veno-venous cooling, which removes blood from a vein (external jugular) and also returns it to a vein (femoral) after cooling, surmounts these drawbacks.[316] A pump, which can be a simple rotary type, is necessary in veno-venous cooling to withdraw the blood from the circulation, move it through the cooling coil, and then return it to the body. A modification of this method inserts the withdrawal cannula through the right auricular appendage into the superior vena cava and pumps the blood back into the femoral vein after passage through a simple cooling coil [255] or a complex refrigerating-warming unit: this form of veno-venous cooling removes the tediousness of cannulating neck veins, which can be of real difficulty in young children.[70] A further modification employs cannulation of both the superior and inferior vena cavae via the right atrial appendage, withdrawing the blood from one vena cava, cooling it, and pumping it back into the other vein. In this manner, operation can be begun at normal temperature and full cardiac exploration carried out to complete the diagnosis before making the decision as to the use of hypothermia; if operation under hypotliermia is then deemed advisable, cannulation of the vena cavae and cooling can be carried out.[69] A final form of direct blood stream cooling, veno-arterial, consists of withdrawing blood from one of the large systemic veins and, after passing the blood through a cooling unit, pumping it back to the patient through an intra-arterial catheter. This technique increases coronary blood flow, and in the experimental animal results in a striking improvement in heart action, as well as a reduced incidence of ventricular fibrillation, during ventricular cardiotomy.[348]

Direct blood stream cooling is without question the most rapid of all the methods of cooling, and rapid cooling has been considered desirable by some in view of the fact that the coronary blood flow during hypothermia undergoes a precipitate fall while the body temperature is being lowered from 36 to 28 C., and then at temperatures below 25 C. remains disproportionately high in spite of a falling aortic blood pressure. This danger period of precipitate reduction in coronary flow can be circumvented by the rapid cooling inherent in the pervascular cooling techniques.[70] Rapid cooling of the blood stream directly also obviates the intense body reaction to cold evoked by surface cooling, since the temperature of the body core is reduced immediately, thus depressing endocrine and hypothalmic activity almost at once. Hence, both reflex peripheral vasoconstriction of the skin vessels, due to contact with a cold stimulus, and shivering, due to temperature gradients, are in large measure avoided by the pervascular technique. Direct blood stream cooling is not without major disadvantages, however: it requires traumatic cannulation of major vessels of the body, employs a complicated pump and cooling coil that can be added worries in an already complicated technique, and it may cause damage to the formed elements of the blood when the latter is passed through a pump and system of coils.

Adjunctive Measures to Cooling. The fact that progressive hypothermia will, at sufficiently low body temperatures, lead to either ventricular fibrillation or cardiac asystole, and the fact that these events will occur at higher body temperatures when circulatory occlusion is superimposed upon hypothermia, have indu-

cated the need to support cardiac function [252] if longer periods of circulatory occlusion than are presently permissible are to be employed as clinical techniques. The protective effect of a well-maintained coronary flow in hypothermia induced by a simple veno-arterial pump circuit has already been noted,[347] suggesting that myocardial failure during hypothermia can be attributed to inadequate myocardial oxygenation brought about by diminished coronary flow and progressive desaturation of the blood supplied to the coronary arteries during inflow occlusion.[322] The use of arterial transfusion,[93] or the administration of oxygenated blood by gravity from a simple reservoir into the root of the aorta above the occlusive clamp, during circulatory occlusion under hypothermia will provide an indirect coronary flow [381] which will almost double the permissible occlusion time.[71] The use of heparinized blood [375] is preferable to the use of citrated blood for this purpose, since it won't add to the acidosis usually associated with periods of inflow tract occlusion.[120] The protection provided for the heart with this method has brought to the forefront the problem of cerebral damage during circulatory occlusion under hypothermia,[320] and there is evidence that under the circumstances of prolonged circulatory occlusion not only the heart but also the brain must be perfused with oxygenated blood.[132] In fact, the safe period for circulatory occlusion in the hypothermic dog can be extended from twenty-five minutes when coronary perfusion alone is employed, up to forty minutes by the use of both coronary perfusion and carotid perfusion.[328]

The use of coronary perfusion, carotid perfusion, hypothermia, and circulatory occlusion, all together, is a combination of technical maneuvers awesome in its complexity, and not unreasonably perhaps has led to the logical extension of combining hypothermia with a pump-oxygenator.[169] There has been reluctance to combine the risks of two dangerous procedures, but in fact the combination permits the use of moderate, rather than the more dangerous deep, hypothermia,[307] and a simple low-flow pump-oxygenator which avoids the complications inherently produced by large capacity pump-oxygenators.[308] With this technique, both the heart and the lungs can be bypassed, by appropriate clamping of the great veins and the aorta, and the heart thus rendered bloodless prior to cardiotomy for the performance of intracardiac operations, while the circulation to the rest of the body is maintained by the pump-oxygenator.[171, 390] The development of extremely efficient blood heat exchangers [75] permits rapid and highly controllable cooling and rewarming (1 degree C. fall in body temperature per minute) [76] at low blood flow rates (20–40 cc./kg. of body weight).[359] Such a combination of moderate hypothermia and a low-flow pump-oxygenator will allow the bypassed, contracting heart to be safely deprived of coronary flow for longer periods than with hypothermia alone.[172] This time can be extended by the production of elective cardiac arrest since the nonbeating hypothermic heart will withstand periods of circulatory occlusion that cannot be tolerated by a contracting heart at the same level of body temperature.[172] Cardioplegia may be produced by perfusion of the coronary system with potassium citrate,[272] acetylcholine,[283, 419] or a solution of potassium, magnesium and neostigmine,[361, 425] a combination which is believed to aid in the restoration of normal heart beat (which can be decidedly difficult to accomplish in the hypothermic heart).[280]

Individual Organ Cooling. Although the selective cooling of individual organs is related to total body hypothermia only indirectly, these methods are attracting increasing laboratory interest and may become of clinical utility in the future.

Selective brain cooling was employed by Temple Fay almost twenty years ago, for the treatment of head injuries and instances of postoperative cerebral edema, by constant irrigation of the surface of the brain with cold saline through burr holes.[146] More recently, differential brain cooling has been accomplished by a form of direct blood stream cooling which requires doubly-cannulating the carotid artery, directing the blood through a cooling coil, and then pumping the cold blood back through the distal tubing in the carotid artery.[305] With this technique it is possible to produce differential cooling of the brain to 14 C. (internal jugular blood temperature) while the general body temperature remains

above 31 C.[226] Thus, maximal brain protection is accomplished at a heart temperature that is well above the fibrillatory range. Brain cooling to these temperature levels is not without danger[352] however, and cooling below 12 C. can result in central nervous system defects.[305] In addition to brain temperature, the other important factor is perfusion flow, or pressure,[420] which must be closely aligned with systemic arterial blood pressure to avoid the production of high systemic venous pressures, and consequent cerebral edema and cardiac failure.[421]

Selective visceral cooling of abdominal organs also has been accomplished, by placing cooling coils around the liver of dogs[80] or wrapping a thin-walled plastic bag as a cooling jacket around the kidney;[388] and both renal[48] and hepatic[209] surgery have been accomplished clinically in isolated instances with localized organ hypothermia.

Conduct of Hypothermia: The rate of cooling in the production of hypothermia will depend mainly upon the size and body build of the patient, the presence or absence of shivering and vasoconstriction, and the method of cooling. Rapid cooling is generally favored, not only for surgical convenience and to minimize the effect of cooling on coronary flow,[39] but also to decrease the risk of frost bite or tissue damage during surface cooling. However, rapid cooling can produce tissue temperature gradients, and it has been postulated that the effect of cold blood upon a relatively-warmer myocardium may predispose to ventricular fibrillation; furthermore, the downward "drift" of body temperature which occurs after surface cooling is discontinued (usually to the extent of about two-thirds the number of degrees the temperature has been lowered at the time cooling is discontinued) is likely to be greater if cooling has been rapid, and may lower body temperature into the range (below 28 C.) in which serious cardiac arrhythmias are common.[408] During the course of the induction of hypothermia, "cold narcosis" supervenes, as previously noted, and the requirements for anesthesia are decreased during hypothermia.[189, 362]

Monitoring. Much of the complexity associated with the techniques of hypothermia is due to the necessity of monitoring several physiological moieties and the fact that such monitoring must be from the core, rather than the surface, of the body in order to provide information of value. A variety of electrical thermocouples are available[92, 189, 201] which will allow continuous readings of body temperature, and the multichannel models of these thermometers permit readings to be made from a number of different body sites. It has been shown that thermal gradients exist throughout the vascular system during normothermia,[207] and that such gradients both exist and may even be accentuated during hypothermia.[199, 389] Studies of these gradients reveal that temperatures recorded from the lower third of the esophagus bear a closer correlation to both the true core temperature[100, 189] and the temperature of the cerebral cortex[199, 389] than do rectal temperatures. Indeed rectal temperatures fall more slowly than esophageal temperatures during cooling,[100] and there may be a difference of up to 4 degrees C between the readings at the temperatures of moderate hypothermia employed today.[389]

In similar fashion, adequate readings of arterial blood pressure must also be made from the core rather than the shell of the body, inasmuch as the intense vasoconstriction precipitated by surface cooling may cause a "clinical disappearance" of the blood pressure after a fall in body temperature of as little as 1 degree C.[50] When blood pressure is monitored by an intra-arterial pressure transducer, it becomes evident that not only may the pressure be recordable, but frequently there may even be a rise rather than a fall.[50, 339]

Electrocardiographic monitoring has been almost routine during the clinical conduct of hypothermia, and in view of the disturbing cardiac effects of hypothermia, there is no doubt ample justification for this monitoring. The electroencephalogram, however, has been thought by some to be a more sensitive indicator of cerebral anoxia,[94, 402] particularly during cardiac manipulations or total circulatory occlusion,[259, 306, 358] and therefore perhaps reflects changes of the circulation to other vital organs in a more precise manner than does the electrocardiogram. Monitoring of the biochemical changes of the body during hypothermia is perhaps the best indication of the state of the circulation to the tissues of the

body.[410] Changes in the blood *p*H and carbon dioxide tension are of particular concern, because of the possible relationship of acidosis to the onset of ventricular fibrillation: indeed, in at least one clinic, a falling *p*H is sufficient indication to stop the operation until the reestablishment of normal acid-base equilibrium.[57] It should be emphasized that correction factors for the physicochemical effects of low temperatures must be applied to estimations of both blood *p*H and blood gas tensions during hypothermia.[121, 370]

Ventilation. Ventilation, of course, is a major factor in the causation of acid-base changes, and the progressive respiratory depression which occurs during hypothermia tends to produce a falling *p*H and acidosis. For this reason, many clinicians have insisted on hyperventilation during hypothermia in order to combat the onset of respiratory acidosis.[399] Others are not in accord with the belief that hyperventilation is a necessity, pointing out that the operative procedure may be a major factor: hyperventilation may be essential during cardiac surgery with total circulatory occlusion, but during hypothermia for neurosurgery, with a closed chest and occlusion of only a segment of the circulation, spontaneous respirations may be adequate to maintain normal *p*H.[403] Finally, there are those who fear the production of respiratory alkalosis, thought also to be a factor in the precipitation of ventricular fibrillation, and yet admit the necessity of preventing respiratory acidosis for the same reason. These workers have compromised by employing hyperventilation with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen to maintain a constant *p*H.[248]

Fluid Therapy. There is, as well, considerable disagreement as to the proper fluid therapy during hypothermia. The inability of the body to metabolize glucose during hypothermia[423] may lead not only to hyperglycemia but also to disturbing alterations in blood protein and electrolyte concentrations.[424] On this basis the administration of glucose to the hypothermic patient has been considered a hazard. On the other hand, there is evidence that glucose can increase the contractile force of heart muscle at lowered body temperatures;[164] therefore, the administration of glucose to the hypothermic patient has been considered a necessity by some. The body also shows a decreased tolerance during hypothermia to the high concentrations of citrate, lactate, and phosphate, present in routinely banked blood[198] and the use of freshly drawn, heparinized blood is advocated if transfusion is necessary.

Rewarming. A final consideration in the clinical conduct of hypothermia concerns the problem of rewarming. Slow rewarming following the termination of acute hypothermia is usually considered preferable to rapid rewarming, since the latter appears to increase the danger of "rewarming shock."[51] The same methods employed for cooling are applicable to rewarming: surface, body cavity, or direct blood stream rewarming. Surface rewarming may be by the application of hot water bottles, by immersion in warm water, by circulating warm fluid through refrigerating mattresses or blankets, by blowing warm air in the cold air chamber, or by the use of diathermy coils wrapped around the body.[42, 52] Body cavity rewarming can be accomplished by circulating warm water in the pleural or peritoneal cavities, in an intragastric balloon, or through a rectal tube.[349] Direct blood stream rewarming is easily accomplished by using warm fluid as the media surrounding the extracorporeal cooling coil or in the heat exchanger. The tendency is not to rewarm actively, but to allow spontaneous rewarming which will occur slowly even in the absence of shivering.[414] Indeed, shivering during rewarming should be prevented, since the occurrence of metabolic acidosis will enhance the danger of "rewarming shock,"[145] and chlorpromazine or analgesic drugs are employed to suppress shivering. An overshoot in body temperature may occur following rewarming, the reverse phenomenon to the drift described during cooling and probably due to a similar mechanism.

Clinical Uses

The clinical usage of hypothermia has been predicated upon the almost linear reduction of metabolism, and therefore of oxygen utilization, that occurs as a result of lowered body temperature in the normothermic organism. Hypothermia thus has been employed to permit occlusion of all or part of the circulation during surgical interventions, or to control

catabolic activity in pathologic states during which hypoxic damage is either present or is a distinct possibility. It is perhaps a generalization to state that circulatory occlusion demands deeper degrees of hypothermia than that used for the control of catabolic activity, which often consists more of the prevention of hyperthermia than the production of true hypothermia. It is also a generalization to state that hypothermia for circulatory occlusion during operation is acute hypothermia, whereas hypothermia for the control of catabolic activity is chronic hypothermia that may be maintained for hours, days, or even weeks.

SURGICAL USES: The object of acute hypothermia is to permit circulatory occlusion during surgery by protecting the vital organs of the body for a limited period of time. The duration of this period of permissible circulatory occlusion will depend upon a multitude of factors: chief among them are the depth of hypothermia, the extent of circulatory occlusion, the magnitude and nature of the surgical intervention, and the patho-physiologic condition of the patient.

Cardiac Surgery. The use of acute hypothermia during operations upon the heart permits total circulatory occlusion by decreasing the danger of ischemia to the central nervous system and other vital tissues. Thus it becomes possible for cardiotomy to be performed and definitive operative procedures undertaken within relatively bloodless chambers of the open heart. Many congenital and acquired forms of cardiac defects have been attacked in this manner, including atrial septal defects of both the primum and secundum variety,[25, 221, 251, 394, 398, 399] pulmonary stenosis of both the valvular and the infundibular types,[25, 122, 221, 394, 398, 399] tetralogy of Fallot,[122, 221, 394, 398] aortic stenosis,[250, 397] mitral stenosis,[97] ventricular septal defects,[25] and tumors of the heart.[88] There are, however, definite limitations imposed upon the performance of open heart surgery under direct vision during hypothermia. The danger of ventricular fibrillation is great during this type of surgery, since precipitating factors of this complication include manipulations of the heart, the alterations in circulatory dynamics produced by such operations, and the profound degrees of acidosis which may be produced by total circulatory occlusion. The hazard increases greatly as the body temperature is lowered below 28 C. in the adult or 26 C. in the child. The permissible period of circulatory arrest at these temperatures has been variously estimated as being from five minutes[256] to fifteen minutes,[231] but probably lies in the range from six to eight minutes, with a maximum of ten minutes. These temperature and time limits indicate that only open cardiac procedures which can be completed in ten minutes or less should be done under hypothermia, and it is the consensus, at present, that such surgery would include operations for pulmonary valvular stenosis, pulmonary infundibular stenosis, atrial septal defect (secundum), atrial septal defect combined with pulmonary valvular stenosis (tetralogy of Fallot) and congenital aortic stenosis.

Cardiac procedures which demand more than ten minutes of intracardiac operating time, such as congenital lesions involving the ventricular septum, transposition of the great vessels, and total valvular replacement, demand more elaborate techniques than simple, acute hypothermia. The combination of hypothermia of a safely attainable degree and coronary perfusion of oxygenated blood has been employed in such procedures,[177] and will extend the duration of permissible circulatory occlusion to twelve or fifteen minutes.[381] The even more elaborate combination of hypothermia, low-flow extracorporeal circulation, and cardioplegia, will extend the permissible occlusion time to at least seventeen minutes[61] and will permit repair of intra-auricular septal defects of the difficult ostium primum type, as well as the repair of intraventricular septal defects.[36]

Great Vessel Surgery. Occlusion of the thoracic aorta during normothermia can imperil the functional integrity of the spinal cord,[20, 304, 314] the kidneys[285] and the liver and other abdominal viscera.[212] The permissible occlusion time, however, can be greatly extended by the use of hypothermia, although prolonged occlusion of the thoracic aorta may lead to cardiac failure even though hypothermia affords complete protection for the spinal cord, kidney, and viscera.[176] Hypothermia has been employed clinically for resection of the aortic arch,[117, 181] the thoracic aorta[180,222] and for operations upon the distal aorta, or its

branches, which require occlusion of the aorta above the renal vessels or celiac axis.

Neurosurgery. The ability to occlude the circulation of the brain with some degree of safety by interruption of the flow through the carotid and vertebral arteries in the neck,[253] or individual arteries within the cranium,[241] has been of outstanding value in neurosurgery. Both ventricular fibrillation,[60] and profound disturbances of hemodynamics following hypothermia,[404] can occur, but are far less likely to be encountered than in cardiac surgery with total circulatory occlusion. Body temperatures of 30 C. provide protection for eight to twelve minutes of occlusion of the cerebral blood flow,[266] but if longer periods are necessary multiple occlusions of shorter duration, with intermittent resumption of flow between occlusions, are safer than a single, prolonged occlusive episode.[259]

Hypothermia has found its greatest use in neurosurgery for the definitive operative attack upon ruptured intracranial, or "berry" aneurysms,[3, 59, 115] but has also been of utility in other vascular lesions such as angiomas,[194] arterio-venous malformations,[254] and aneurysms of the carotid vessels.[55, 128]

The fact that hypothermia also reduces intracranial pressure[344] has led to its use without circulatory occlusion to provide better operative exposure and to diminish trauma during the excision of cerebral tumors,[214, 364] such as meningiomas, [287] glioblastomas,[287] and craniopharyngiomas.[214] It must be emphasized, however, that cerebrospinal fluid pressure is not automatically reduced by hypothermia, if shivering, hypoxia, or hypertension are allowed to occur.[243] This fact has led to the intentional combination of the hypothermic and hypotensive techniques[129] to enhance exposure by further decreasing intracranial pressure[257] as well as to decrease bleeding.[81, 364] It is possible that the addition of hypothermia does increase the safety of the hypotensive techniques as has been claimed,[125] but it is probable that induced hypotension increases the risk in hypothermia. It is likely that a sudden hypotension will embarrass the coronary circulation and jeopardize the myocardium, in view of the reduced coronary flow already present during the hypothermic state.[60]

Cerebrospinal fluid pressure may be increased following craniotomy under hypothermia,[246] and for this reason not only is active rewarming often avoided, but moderate or light hypothermia actually continued into the postoperative period to prevent cerebral edema, hyperpyrexia, and postoperative coma.[214]

General Surgery. The deleterious effects of temporary ischemia to the liver,[40, 174, 223] kidney,[187] and intestines[271] can be ameliorated by hypothermia, and the technique has been of value in partial hepatectomy,[210] excision of renal tumor,[187] and the performance of portacaval shunt.[93]

Hypothermia also has been applied to a variety of other surgical procedures to minimize the stress[163] of extensive dissections[9, 288] or to lower metabolism and combat hyperpyrexia in toxic states[64] or "poor-risk" patients.[8, 65] The beneficial effects possible in the latter group of patients, however, must be weighed against the fact that they withstand blood loss poorly[289] and are prone to develop hypovolemia, shock, and cardiac failure during the rewarming period.[127]

THERAPEUTIC USES: Although total body hypothermia was employed a decade ago primarily as an adjunct to operative intervention, the predominant use of hypothermia today is not to facilitate surgery but as a therapeutic measure to prevent hypoxic damage, particularly to the brain, and to control catabolic activity in a variety of pathological conditions. For these purposes, hypothermia is generally light in degree or may merely consist of the prevention of hyperthermia. However, hypothermia is also generally maintained for considerable periods of time in such instances, quite in contrast to the duration of acute hypothermia employed for operative procedures. It is worth pointing out that the physiologic changes during chronic hypothermia warrant further elucidation, since they are not necessarily the same as those seen during short-term hypothermia.[127]

Hyperpyrexia. The use of cooling to combat fever is probably as old as the practice of medicine itself, but simple sponging or fanning of the surface of the body are often inadequate for this purpose and may require supplementation with the techniques—or modification of the techniques—of total body hypothermia.

Surface cooling, produced by a refrigerating mattress or blanket combined with the use of chlorpromazine to combat shivering and produce vasodilation,[249] is the most popular method, and the body temperature is reduced to only 33–35 C.[325] Hypothermia of this type has been employed with laudable results in critically ill febrile patients with encephalitis,[131, 219] poliomyelitis,[277] pneumonia,[235] and other infections,[217] as well as in thyrotoxicosis,[62, 211] eclampsia,[263] and heat stroke. In these instances, of course, the therapy is directed merely at the hyperpyrexia and not at the underlying disease process, but there is some experimental evidence to indicate that, in certain forms of bacterial infection at least, hypothermia may enhance the antibacterial defenses of the organism,[136] possibly by a decrease in the rate of bacterial multiplication at lower temperatures.[23, 422] Following the discontinuance of hypothermia, clinical exacerbation infection has been noted in some instances.

Cerebral Injury. Hypothermia is capable of protecting the brain in head injuries by limiting the response to trauma,[343] and a major use of hypothermia has been for the treatment of cerebral injury.[278, 363] The technique has generally consisted of surface cooling and moderate doses of chlorpromazine to induce a hypothermia of 34–30 C. This usage has been expanded to include not only head injuries,[243, 261] but also spontaneous cerebral hemorrhage,[208] postoperative cerebral edema,[365] and other forms of cerebral ischemia which lead to hyperpyrexia with tonic fits superimposed on the decerebrate rigidity. Cooling is maintained for prolonged periods of time in these instances (in one patient intermittently for more than five months[351]), and any recurrence of neurological signs during the warming period is indication for recooling.

Cardiac Arrest. A most important extension of this use of hypothermia in cerebral injury is to prevent brain damage from ischemia following cardiac arrest. It is quite conceivable that this may become one of the major indications for the method in relation to anesthesia. Injury to the central nervous system following cardiac arrest is caused by anoxia. The principal effects of the latter are direct injury to nerve cells and the appearance of cerebral swelling which, by increasing intracranial pressure, leads to a vicious cycle of further anoxia followed by further vascular injury and further swelling. Hypothermia will protect the brain against such anoxic injury and also reduce intracranial pressure by reducing brain volume, and if applied to patients exhibiting signs of severe central nervous damage following successful cardiac massage, can aid in promoting either complete recovery or at least in minimizing the residual neurologic deficit.[416]

Asphyxia Neonatorum. Results with experimental asphyxia in newborn laboratory animals have demonstrated that a 10 degree C. reduction in body temperature will provide complete protection against an asphyxial exposure which is lethal for litter-mate controls.[276] Hypothermia (22 C.) can also maintain the apneic nonviable premature human fetus alive for hours.[275] Hypothermia produced in neonatal asphyxia pallida by merely placing the asphyxiated infant in running cold (10 C.) tap water has effected spontaneous respirations in from fourteen to seventy-nine minutes after birth, at body temperatures ranging from 34–23 C., following failure of all other resuscitative attempts.[415] All the infants so resuscitated have had normal acoustic acuity when tested during the first few days of life, in distinct contrast to records obtained from other babies who had recovered from severe asphyxia with or without neurological symptoms. It would appear from this study that hypothermia may become a technique of outstanding utility in the resuscitation of the badly asphyxiated newborn.

Hematemesis. The secretory activity of the gastrointestinal tract is markedly reduced by hypothermia.[354] Local gastric cooling by an intragastric balloon to temperatures of 17–20 C. will depress gastric secretion substantially without evidence of injury to the gastric mucosa.[411] This technique has been employed clinically to control massive hematemesis of acid-peptic origin, and it is considered by its protagonists to be a measure of value in readying patients with active gastric hemorrhage for operation by inhibiting peptic activity, arresting hemorrhage, and permitting restoration of a fairly normal blood volume.

Experimental Applications to Clinical Problems. Laboratory investigations into the application of hypothermia to a number of clinical

problems are of sufficient possible future interest to warrant mention. Some workers have been attracted by the ability of hypothermia to prevent the response to stress, and to lower metabolic activity, in relation to the therapy of shock state. They have concluded that lowering the body temperature after the onset of an otherwise irreversible shock due to hemorrhage exerts a significant therapeutic effect.[301, 317] Most of these studies of hemorrhagic shock have been performed with the Fine modification of the Wiggers method of controlled hemorrhagic hypotension,[200, 316] however; and it has been pointed out that this technique studies artificially controlled hypotension but not hemorrhage *per se*.[118] When a single acute hemorrhage is employed to produce shock experimentally, hypothermia exerts a decidedly deleterious effect.[151] Studies of the effect of hypothermia on traumatic shock have led to the similar conclusion that there is no rationale for its use in established shock or in the prevention of shock.[224]

There has also been considerable interest in hypothermia as an adjuvant to therapy in burns, since the metabolic rate is definitely lowered, and water, electrolytes and plasma accumulations are diminished in the burned areas;[267] but there is no clear-cut evidence that cooling can either prevent development of shock or effect prolongation of life following extensive burns.

The possibility of employing hypothermia in the therapy of coronary disease has intrigued some workers. The primary aim of treatment in acute coronary occlusion with myocardial infarction is to reduce heart (and body) work and oxygen consumption, and since these are both effects produced by hypothermia, it has seemed reasonable to expect cooling to be of benefit. In point of fact, however, several studies of the use of hypothermia in experimentally produced coronary occlusion have demonstrated conclusively that hypothermia is not only without benefit, but even increases the mortality rate considerably in comparison with control animals subjected to an identical artificially-produced coronary occlusion.[116, 269, 278] Ligation of a major branch of the coronary arterial system in a laboratory animal is scarcely comparable to occlusive coronary disease in the human patient, but these studies have led one observer to comment that body cooling has no place in the treatment of acute coronary arterial occlusion and that, further, the use of hypothermia as an ancillary method in "poor-risk" patients is fraught with danger if coronary arterial insufficiency already exists, whether from organic changes in the coronary arterial tree or from diminished filling due to hemorrhage or shock.[278]

Complications

The production of the hypothermic state bears with it all the hazards ordinarily associated with anesthesia, surgery, and the pathophysiologic conditions of the patient in whom hypothermia is being induced, but in addition it may be complicated by specific hazards induced by hypothermia itself. It must be emphasized, however, that these several factors contributing to the production of complications are not entirely separable: complications, for instance, that are due to a specific surgical manipulation, or the particular disease condition suffered by the patient, might not have been precipitated in the absence of hypothermia. Similarly, they also might not have been precipitated by hypothermia itself in the absence of that specific surgical manipulation, or that particular disease condition suffered by the patient. As an example, intentional circulatory arrest for ten minutes induced in dogs during hypothermia results in a severe derangement of hepatic function and structure which is not seen in control dogs cooled to the same temperature without circulatory arrest.[6]

Ventricular Fibrillation. The most dramatic and certainly the most serious complication of hypothermia has been ventricular fibrillation, and a tremendous amount of effort has been expended in an attempt to elucidate the factor(s) which induce this arrhythmia. Without deprecating either the seriousness of this complication or the danger of its occurrence, it should be stressed that in light or moderate hypothermia that is not employed for cardiac surgery, the risk of fibrillation is far less than might be expected from the amount of publicity that has been accorded this arrhythmia. For although innumerable factors have been implicated in the production of ventricular fibrillation during hypothermia,[24] without ques-

tion the major causes have been: (1) a level of body temperature below 28–26 C., (2) total circulatory occlusion for 10 or more minutes, and (3) cardiotomy,[290] particularly left ventriculotomy. These conditions set the background for the development of accelerating discharges from ectopic centers in the ventricle, and such ectopic foci occur most easily in the diseased heart[333]—which compounds the problem in many patients undergoing cardiac surgery during hypothermia. Other factors may be contributory to the development of ventricular ectopic discharges: (1) disturbed myocardial calcium/potassium balance, (2) changes in blood *p*H, (3) increased activity of cardiac sympathetics, and (4) increased amounts of circulating catechol amines.

One of the factors involved in the pronounced decrease in fibrillary threshold during hypothermia[103, 311] may well be an ionic imbalance of cardiac muscle, but there is disagreement as to the exact changes that occur in the concentrations of myocardial electrolytes. Potassium has been variously reported as increased,[278] unchanged,[282] or decreased[106] in cardiac muscle during hypothermia, but the results depend upon the experimental procedure employed, the existence of acidosis or alkalosis, and whether or not the heart eventually went into fibrillation. The ion apparently does leave the myocardial cell prior to hypothermic fibrillation,[269] however; and the onset of fibrillation therefore may be due to an altered calcium/potassium balance, inasmuch as cardiac muscle gains calcium,[14] which has been shown to precipitate ventricular fibrillation in the hypothermic state.[178]

Studies of plasma concentrations of these electrolytes are even more inconsistent, and may show a decrease,[33, 398, 382, 400] an increase,[128] or no change[159] in potassium; and either no change[159] or a slight increase in calcium.[128, 380] The assumption has been that a rise of the serum calcium/potassium ratio would produce a similar change within the myocardium, and thus contribute to the onset of fibrillation.

Plasma *p*H appears to be definitely related to ventricular fibrillation and the greatest danger appears to be from a sudden shift of *p*H, since either acidosis or alkalosis can be associated with fibrillation. It has been hypothesized that a change in *p*H may be correlated with a change in the potassium concentration, but the actual mechanisms involved are by no means clear.

There is considerable evidence that increased sympathetic activity and decreased vagal tone are important factors in the occurrence of this serious arrhythmia. Fibrillation in hypothermic animals subjected to inflow occlusion and right ventriculotomy can be prevented by bilateral sympathetic denervation of the heart,[374] high spinal block,[265] sympathetic ganglionic blocking agent (Arfonad),[334] vagal stimulation,[330] or block of the sino-auricular node with a local anesthetic agent.[321, 329, 330]

Catechol amines may be related in similar fashion to ventricular fibrillation, since it is known that epinephrine is a potent fibrillatory agent in hypothermia as well as during normothermia[39] and there is an increase in the levels of circulating epinephrine and norepinephrine in the hypothermic dog.[24] It may be that there is an appreciable accumulation of catechol amines in the inferior vena caval blood during total circulatory occlusion as a consequence of sino-aortic reflexes, and this could explain the high incidence of ventricular fibrillation which occurs soon after the release of occlusion. It is worth noting that physiological situations producing acidosis may also lead to release of catechol amines, which might be a factor in the relationship of low blood *p*H to ventricular fibrillation.

The relationship of myocardial hypoxia to ventricular fibrillation is well known, and undoubtedly important in cardiac surgery during hypothermia with circulatory occlusion, as indicated by the protective effect of coronary perfusion with oxygenated blood during the period of occlusion.[132, 375] The role of hypoxia in the production of ventricular fibrillation during hypothermia not associated with cardiac surgery is probably not large, for although it has been postulated that the displacement of the oxygen dissociation curve to the left during hypothermia might induce hypoxia, coronary arterio-venous differences remain unchanged at temperatures as low as 20 C.[131] There seems little doubt that a reduction in coronary flow occurs during hypothermia,[39,

[133, 220, 352] but there is also abundant evidence that the oxygen demand of the heart is greatly reduced by the low myocardial temperature, the reduced cardiac output, decreased arterial pressure, and the bradycardia, and that these factors reduce the demand for oxygen so much that the curtailed coronary flow presumably remains adequate for the requirements of the myocardium.[21, 22, 39, 191, 220, 310] The situation is quite different, as suggested above, in cardiac surgery with inflow occlusion under hypothermia: in such instances, the ventricles are subjected to diffuse ischemia which may well contribute to the onset of ventricular fibrillation which may develop after occlusion.

The prevention of ventricular fibrillation during hypothermia has necessarily been a consuming concern, and a large number of pharmacologic agents known or suspected to have antifibrillary activity have been explored under conditions of hypothermia,[226] including acetylcholine,[37] neostigmine (Prostigmine),[278] procainamide (Pronestyl),[109] 2-diethylaminoethylisonicotinamide (Ambonestyl),[107, 239] aminoacetic acid (glycine),[31, 32] diphenylhydantoin (Dilantin),[109] β-(2 biphenylyloxy)-ethyl-diethylamine (Dacorene),[109] trimethaphen (Arfonad),[374] procaine,[321] quinidine,[170] ouabain,[16] piperidolate (Dactil),[185] and mephenteramine (Wyamine).[102] Some of these drugs look promising in the laboratory,[84, 278] but it cannot be said that many of them have gained wide clinical usage.

Probably far more important than pharmacologic agents in the prevention of ventricular fibrillation is avoidance of those factors known to produce this arrhythmia. Cardiotomy through the left ventricle may be dangerous, since the development of ectopic foci in the ventricles, coupled with prolongation and variation in the relative refractory period produced by lowered temperature,[15] is of fundamental importance in the production of fibrillation. Temperatures in the fibrillary range (below 28 C.) should be avoided, since the fibrillary threshold of the heart at these temperatures is such that fibrillation can occur spontaneously without stimulation by mechanical manipulation. Considerable effort has been expended to prevent a fall in blood *p*H, and most workers employ hyperventilation for this purpose.[400] Some, however, have added carbon dioxide to the inhaled mixture employed in hyperventilation, on the basis that a respiratory alkalosis will cause as great a shift in blood *p*H, and be just as dangerous, as acidosis.[293] One group has deliberately produced acidosis,[130] on the basis that defibrillation is accomplished most easily at a low blood *p*H. Shivering should be prevented, as it can produce both acidosis and a rise in the serum potassium level,[128] which may disturb the myocardial calcium-potassium ratio and contribute to the precipitation of fibrillation.

The treatment of hypothermic fibrillation has been a frustrating problem, and no ready solution exists to the irreversibility of this arrhythmia in the hypothermic state.[268] The standard methods of defibrillation, which consist of cardiac massage, and if necessary the use of adrenaline, to improve the tone of the heart muscle, followed by electrical defibrillation,[66] may be difficult to accomplish or only momentarily effective,[237] with subsequent return of fibrillation. Fortunately, considerable protection for the brain is afforded by the existence of the hypothermic state,[372] but such protection is limited in duration. Considerable investigation of ancillary measures that will facilitate defibrillation has therefore been undertaken, and laboratory results indicate that some of these techniques may find clinical utility. Prostigmine has antifibrillatory activity in the hypothermic dog, and when ventricular fibrillation occurs in the unprotected animal, coronary perfusion of prostigmine will allow conversion of the arrhythmia to normal rhythm by cardiac massage and electric shock.[319] Potassium, employed to produce intentional cardioplegia, has been successful in stopping ventricular fibrillation in both normothermic and hypothermic dogs, but the diastolic arrest which follows the administration of potassium chloride is extremely difficult to overcome and ventricular fibrillation recurs in a sizable proportion of animals.[241] Hearts which have been defibrillated by the administration of potassium chloride into the left ventricle can be resuscitated from cardiac standstill successfully, however, by the intracardiac injection of sodium lactate followed by equal amounts of Ringer's lactate combined

with cardiac massage,[257] or by the administration of hypertonic glucose[30, 270] or fructose.[207] The beneficial effect of these hypertonic solutions appears to be related to maintenance of normal concentration of the circulating potassium ion in the extracellular fluid and plasma, and deposition of potassium and glycogen in the myocardium.[297] Alternative methods of resuscitation of the potassium-arrested heart have been the perfusion of cold blood[111] or tetraethylammonium chloride[82] into the coronary arteries to prevent the usual high incidence of recurrence of ventricular fibrillation.

Rewarming Shock. A major hazard associated with the immediate posthypothermic period consists of the development of hypotension[149, 192] and acute circulatory collapse that is characterized by tachycardia, diminished cardiac output, and inadequate respirations.[51, 145] The syndrome, which is particularly prone to occur during rapid rewarming,[145] appears to be due to acidosis; and the fact that both the *p*H and the carbon dioxide combining power of the blood are decreased indicates that there is a predominantly metabolic element in the acidosis.[410] For this reason, rewarming shock often results from shivering[144] or following total circulatory occlusion,[68] which of itself produces serious venous congestion leading to gross acidosis and lactacidemia.[201] The prevention of this syndrome therefore is based upon the maintenance of a normal blood *p*H by the prevention of both shivering and vasoconstriction, continuation of adequate ventilation without the production of respiratory alkalosis, and slow rewarming.[144]

Bleeding Tendency. The effects of hypothermia upon the coagulation of blood are of real clinical importance, since disturbance of the clotting mechanism has been one of the major causes of death in surgical interventions performed under hypothermia,[393] but the precise nature of this bleeding tendency is poorly understood. It may be related to the development of a fibrinolytic tendency during total circulatory occlusion,[409] since it is not prevalent in simple hypothermia alone.[70] On the other hand, it may be related to the development of thrombocytopenia,[190] and the administration of small doses of heparin prior to cooling has been advocated as a method to minimize thrombocytopenia and eliminate bleeding tendencies.[413] It is possible that some instances of reactionary hemorrhage which have been attributed to a defect in coagulation actually may have been due to a failure to ligate all bleeding points when the surgical wound has been closed before rewarming and during hypothermic hypotension.

Tissue Injury. The techniques of surface cooling can produce injury to the skin, the subcutaneous tissues, or the peripheral nerves, and while such lesions are seldom if ever lethal, they do represent very real complications of this form of cooling. Cold skin is particularly liable to injury by heat, and skin burns have resulted from the warm water mattress, hot water bottles, heat cradles, and following diathermy.[86, 189, 398] Usually such burns are of second degree and small in size.

A diffuse firmness and solidification of the subcutaneous tissues of the thighs and the panniculus of the abdomen, associated with larger hard indurated lumps, has been described in infants following hypothermia.[54, 145] The pathogenesis of this lesion appears to be based upon the fact that the fat of young children contains a relatively low percentage of certain fatty acids, and as a consequence has a relatively high melting point in comparison with the fat of the adult; thus, solidification can occur in infant fat at temperatures far above those necessary to produce solidification in adult fat.[2] Subcutaneous fat necrosis has progressed to actual tissue slough in some of these patients.

The most disturbing of these local injuries resulting from surface cooling his been postoperative peripheral nerve dysfunction in the extremities. These neuropathies have involved both sensory and motor elements; and while in some instances the syndrome appeared to fit a definite pattern, such as peroneal or lower brachial plexus palsy, in others it has been bizarre. The exact cause of these lesions has not been determined, but it has been postulated that the hypothermic nerve may be prone to pressure injury.[393]

Cerebral Ischemia. Actual brain damage from the effects of cold *per se* does not occur at the temperatures of moderate hypothermia which are employed clinically,[305] but there is real danger to the brain because of the hazard of cerebral ischemia following intentional cir-

culatory occlusion.[350] It is ironical that this disastrous complication should occur when hypothermia is employed specifically to prevent such pathology, and would seem to indicate either that the permissible occlusion times have been overestimated [227] or that these limits have been exceeded in certain instances.

Organ Damage. There is a widespread impression that hypothermia can effect metabolic depression without effecting alteration of morphologic structure. The statement has been made that in hypothermia above 20 C. no specific cellular pathology occurs within periods of several hours, and that, further, the temperature range free of organic disturbances may extend much lower.[302] The experimental evidence in regard to organ damage, however, while not entirely clear, nevertheless does not support this thesis. Few would disagree with the contention that hypothermia to low temperature levels can be tolerated by individual organs [412] or even, as will be seen, by the entire organism, with restoration of function on rewarming. The question of morphological change, and particularly cellular damage, however, is something else. Certainly the combination of hypothermia total circulatory occlusion, and cardiac surgery, can produce pathologic cardiac alterations consisting of localized fibrinous pericarditis and necrobiotic myocardial changes.[356] These findings might be anticipated in view of the trauma to the heart involved in such maneuvers. Much more surprising is the fact that multiple foci of necrotic muscle fibers can be produced by moderate hypothermia alone, and that these distinct areas of necrosis show the various stages of organization known to occur in the development and healing of experimental myocardial infarctions.[355] It has been suggested that these focal disturbances in the myocardial blood supply may contribute to the conduction disturbances encountered during hypothermia, and may even bear a relationship to the ectopic foci known to develop in the cold heart.

More drastic changes have been demonstrated at the cellular level by histochemical techniques (following cooling to body temperature levels that are not far beyond the point generally regarded as ideal for surgery) including accumulation of fat in the liver, kidney, and adrenal glands; depletion of glycogen in the liver; and vacuolization of the granular cells of the zona reticularis of the adrenal cortex.[238] Other investigations undertaken to confirm these findings, however, have failed to reveal alterations in the fat content of the adrenals, kidneys, and liver, or significant changes in the succinic dehydrogenase, cytochrome oxidase and alkaline phosphatase activity, in the heart, liver, or kidneys, even in hypothermia maintained at lower temperatures (18–20 C.) and for longer periods of time (two to twenty-three hours).[228] It has been concluded that hypothermia is not attended by specific pathologic alterations which might be interpreted as resulting from anoxia, and that such changes as have been noted are in no way correlated with survival.[153]

It seems obvious that the conflicting evidence on this important question of organ damage necessitates further work on the subject, for if investigation is carried one step further to include more sophisticated biochemical analyses, shifts in the temperature kinetics of enzyme systems can be demonstrated during hypothermia,[184] and it becomes essential to know whether such shifts are totally reversible on rewarming or represent true damage as a result of cold.

Present Status

In the short span of the decade that has seen major clinical utilization of the techniques of total body hypothermia, vast changes have occurred in the applications of this modality. The use of hypothermia for cardiac surgery has been, first, championed; then, abandoned in favor of extracorporeal circulation in certain instances; and finally, now, is being combined with the latter technique to provide a method with greater promise than either technique alone. The use of hypothermia for neurosurgery, particularly in ligation of intracranial aneurysms and excision of vascular tumors, has first displaced the techniques of "controlled hypotension," and now is itself being displaced, in some clinics by the use of urea and hyperventilation. The therapeutic uses of chronic hypothermia to control catabolic activity in pathologic states and to combat the deleterious effects of hyperthermia, barely mentioned as an application ten years ago, have become far

more important and widespread in clinical usage than acute hypothermia for surgery. Hypothermia, in short, has been a field of extremely rapid change, and there is no reason to believe that there will not be even more far-reaching changes in the future—on the contrary, there seems every good reason to believe that further changes are not only inevitable, but are in fact already taking place with the advent of techniques for profound hypothermia.

It has long been known that hibernating mammals (ground squirrel, hedgehog, hamster, bat) can survive artificial cooling which lowers the deep body temperature to nearly 0 C. and that they recover spontaneously in a warm environment; but it has also been thought that death is inevitable in homeotherms cooled to 10–19 C., inasmuch as there will be cessation of both respiratory and cardiac activity (in contrast to hibernators, who continue a slow heart beat and breathing even at these low temperatures). The demonstration that, by using special methods of cooling and rewarming, rats may be full revived after their rectal temperatures have been lowered as far as 1 C. has opened up an entirely new area in hypothermia. The animals were cooled in two stages, first to 20 C. in small containers so that they were exposed to a progressive fall in oxygen tension and a rise in carbon dioxide tension, and then by covering them with crushed ice, to colonic temperatures of 1 C. Respirations ceased at about 9 C. and heart beat at about 6 C. Revival could not be accomplished by merely rewarming the body and carrying out artificial respiration; but if the circulation was first re-established by applying heat locally to the cardiac area, combined with artificial respiration, anoxia during rewarming was avoided and recovery was possible.[32]

These investigations have rearoused interest in the possibilities of profound hypothermia, and cats have been successfully cooled to body temperatures below 15 C. using this method of hypercapnia and hypoxia.[28] The rate of body cooling, and the oxygen and carbon dioxide concentrations, are critical parameters in this technique, however, which are extremely difficult to control in an animal as large as the cat, and other methods for the production of profound hyperthermia are under current investigation. Surface cooling to body temperatures between 10 C. and 0 C., with successful resuscitation, has been achieved by refrigerating blanket and artificial ventilation with 5 per cent carbon dioxide—95 per cent oxygen in the rat,[292] the dog,[294] the monkey[293] and even in man.[296]

But perhaps the most promising approach to profound hypothermia with cessation of heart beat is to be found in the combination of hypothermia and extracorporeal circulation with a pump oxygenator.[169] The inclusion of a heat exchanger in the extracorporeal circuit will permit rather precise control of cooling and rewarming, which is essential to the production of asystole and subsequent restoration of normal rhythm without the development of fibrillation.[229] The production of profound hypothermia by extracorporeal circulation has other notable advantages, chief amongst which is the fact that the tremendous reduction of the organism's total oxygen requirement avoids the need for a heart-lung machine capable of delivering high outputs of oxygenated blood and permits the use of a simple pump oxygenator that requires much less donor blood to prime, needs a far lower dose of heparin to prevent clotting within the circuit, and minimizes the damage to the formed elements in the blood itself.[171] Oxygenation exceeds by far the oxygen requirement during extreme hypothermia, and a degree of oxygenation can be achieved in which the arterio-venous oxygen difference is less than one-half volume per cent.[173] Cardiac arrest of one hour's duration during hypothermia at 0 C. has been achieved in dogs with this technique followed by survival,[168] and open cardiotomy of the left heart has been performed at temperatures below 10 C. in the dog without the occurrence of anoxia or ventricular fibrillation.[170] The technique has been successfully employed for operation on a tetralogy of Fallot at an esophageal temperature of 9.3 C. to produce cardiac standstill without the use of a cardioplegic agent, and the patient made an uncomplicated recovery.[126]

A further modification omits the artificial oxygenator by utilizing the patient's own lungs for their normal function of oxygenation, but requires two blood pumps (one to by-pass each ventricle) and therefore two extracorporeal circuits.[124, 313] This method has been

used in three children operated upon during hypothermia to 15 C. with periods of cardiac arrest up to a forty-five minutes during the repair of ventricular defects. Ventricular fibrillation did not occur, hemolysis was negligible, there were no significant biochemical changes, and the two survivors showed no evidence of neurological or other damage.[122]

Cooling to low levels of body temperature by these extracorporeal techniques produces temperature gradients that are in many respects the reverse of those seen in surface cooling, since the core of the body cools first and the shell, or surface, later. The temperature of the blood falls immediately, of course, followed by the temperature of the heart and esophagus. The temperatures of the liver and kidneys fall more slowly, and the brain and colonic temperatures lag still farther behind. Slowest of all to cool are the limb muscles.[272]

Cardiac action ceases at 13–18 C. (hepatic temperature, selected as the most satisfactory index of cooling), and reappears on rewarming at 14–18 C. Ventricular fibrillation, when it does occur, is easily treated by "cold conversion" (*i.e.*, recooling to asystole). Electrical waves are recordable in the heart even at temperatures as low as 5 C., but electroencephalographic waves disappear at 12–15 C. A considerable metabolic acidosis develops during profound hypothermia; plasma potassium falls slightly; and plasma sodium remains unchanged. There is complete suppression of urinary output during cooling, circulatory arrest, and the early rewarming period, with return of urine formation during the later stages of rewarming.[230]

These attainments of profound hypothermia are exciting developments, not merely for cardiac surgery, but as well for the innumerable other vistas opened up in relation to such problems as organ transplantation, reconstructive surgery, and the attenuation of fulminating disease processes. Thorough realization of these potentials, however, will require that "haste" be made slowly. Already the use of profound hypothermia with extracorporeal circulation has brought such a rapid and vigorous advance of open-heart surgery that successful clinical experiences have far out-distanced fundamental observations as to the nature of this changed physiological state. A number of problems on which there is little or no information at the present time have been raised by lowering body temperature to these profound levels. What, for instance, is the extent of the increase in blood viscosity, and what is the effect of this increase in blood viscosity on capillary flow? What is the effect on enzyme activity, and is the effect completely reversible on rewarming?

Several years ago, in reviewing the progress in hypothermia, Brooks and Hoffman made the following comments as to the urgent need for additional physiological investigations: "It should be stated, without implied criticism of those who have made contribution to this field, that fuller studies are needed. Additional multiple recordings and analyses are required before conclusions can be drawn about many matters. . . . Despite the vast amount of work already done, little is as yet known concerning the action of hypothermia. It is abundantly evident, however, that unless future experiments are well conceived, carefully done, and more extensive, they will add little to our present knowledge. . . . It is felt that the individual cell and specific reactions must be studied more thoroughly; that the action of hypothermia on membrane function and on the contractile process should be determined; and that a more extensive study than has yet been attempted of the functional changes in the intact heart during hypothermia must be undertaken by groups qualified and equipped to study many aspects of physiology:" [73]

These comments have lost none of their validity with the advent of profound hypothermia.

REFERENCES

1. Adams, J. E., Elliot, H., Sutherland, V. C., Wylie, E. J., and Dunbar, R. D.: Cerebral metabolic studies of hypothermia in the human. Surg. Forum 7: 535, 1957.
2. Adams, J. E., Foster, J. H., Faulk, W. H., and Scott, H. W., Jr.: Experimental production of subcutaneous fat necrosis by general hypothermia; relation to chemical composition of fat, Surg. Forum 5: 556, 1955.
3. Adams, J. E., and Wylie, E. J.: Value of hypothermia and arterial occlusion in the treatment of intracranial aneurysm, Surg. Gynec. & Obst. 108: 631, 1959.
4. Adolph, E. F.: Oxygen consumptions of hypothermic rats and acclimatization to cold, Am. J. Physiol. 161: 359, 1950.

5. Adolph, E. F.: Responses to hypothermia in several species of infant mammals, Am. J. Physiol. 166: 75, 1951.
6. Albert, S. N., and Fazekas, J. F.: Cerebral hemodynamics and metabolism during induced hypothermia, Anesth. & Analg. 35: 381, 1956.
7. Albert, S. N., Shibuya, J., and Knight, J. F.: Simple cooling unit for hypothermia, Anesth. & Analg. 36: 73, 1957.
8. Albert, S. N., Spencer, W. A. Boling, J. S., and Thistlethwaite, J. R.: Hypothermia in management of poor-risk patient undergoing major surgery, J. A. M. A. 163: 1435, 1957.
9. Albert, S. N., Spencer, W. A. Eccleston, H. N., Jr., Shibuya, J., Albert, C. A., and Thistlethwaite, J. R.: Utilization of moderate hypothermia as adjunct to general anesthesia for extensive surgical procedures, Anesth. & Analg. 35: 570, 1956.
10. Alexander, L.: Treatment of shock from prolonged exposure to cold, especially in water, Washington, D. C., Office of the Publication Board, Department of Commerce, Report No. 250, 1946.
11. Andersen, M., and Nielsen, K. C.: Renal function under experimental hypothermia in rabbits, Acta med. scandinav. 151: 191, 1955.
12. Andjus, R. K., and Smith, A. U.: Reanimation of adult rats from body temperatures between 0 and + 2 C., J. Physiol. 128: 446, 1955.
13. Angelakos, E. T.: Distribution of terminal temperatures in hypothermic dogs, Proc. Soc. Exper. Biol. & Med. 97: 107, 1958.
14. Angelakos, E. T., Deutsch, S., and Williams, L.: Sensitivity of hypothermic myocardium to calcium, Circulation Res. 5: 196, 1957.
15. Angelakos, E. T., LaFloret, E. G., and Hegnauer, A. H.: Ventricular excitability and refractoriness in hypothermic dog, Am. J. Physiol. 189: 591, 1957.
16. Angelakos, E. T., Torres, J., and Driscoll, R.: Ouabain on hypothermic dog heart, Am. Heart J. 56: 458, 1958.
17. Anlyan, F., Hastings, E. P., and Angelakos, E. T.: Comparison of anesthetics on incidence of ventricular fibrillation in experimental hypothermic ventriculotomy, ANESTHESIOLOGY 19: 213, 1958.
18. Armstrong Davison, M. H.: Evolution of anaesthesia, Brit. J. Anaesth. 31: 134, 1959.
19. Axelrod, D. R., and Bass, D. E.: Electrolytes and acid-base balance in hypothermia, Am. J. Physiol. 186: 31, 1956.
20. Badeer, H.: Influence of temperature on S-A rate of dog's heart in denervated heart-lung preparation, Am. J. Physiol. 167: 76, 1951.
21. Bädeer, H.: Influence of oxygen on hypothermic cardiac standstill in heart-lung preparation, Circulation Res. 3: 28, 1955.
22. Badeer, H.: Role of hypoxia in hypothermic cardiac arrest in heart-lung preparation, Am. J. Physiol. 183: 119, 1955.
23. Badeer, H.: Effect of hypothermia on oxygen consumption and energy utilization of heart, Circulation Res. 4: 523, 1956.
24. Badeer, H.: Ventricular fibrillation in hypothermia; review of factors favoring fibrillation in hypothermia with and without cardiac surgery, J. Thoracic Surg. 35: 265, 1958.
25. Bailey, C. P., Cookson, B. A., Downing, D. F., and Neptune, W. B.: Cardiac surgery under hypothermia, J. Thoracic Surg. 27: 73, 1954.
26. Balch, H. H., Noyes, H. E., and Hughes, C. W.: Influence of hypothermia on experimental peritonitis, Surgery 38: 1036, 1955.
27. Barnard, C. N.: Hypothermia; method of intragastric cooling, Brit. J. Surg. 44: 296, 1956.
28. Battista, A. F.: Deep hypothermia in cats, Am. J. Physiol. 196: 354, 1959.
29. Beattie, E. J., Jr., Adovasio, D., Keshishian, J. M., and Blades, B.: Refrigeration in experimental surgery of aorta, Surg. Gynec. & Obst. 96: 711, 1953.
30. Beavers, W. R.: Hypothermia: effects of hypertonic solutions on incidence of ventricular fibrillation, Am. J. Physiol. 196: 705, 1959.
31. Beavers, W. R., and Covino, B. G.: Immersion hypothermia: effect of glycine, Proc. Soc. Exper. Biol. & Med. 92: 319, 1956.
32. Beavers, W. R., and Covino, B. G.: Aminoacetic acid (glycine) as antifibrillary agent in hypothermia, A. M. A. Arch. Surg. 75: 776, 1957.
33. Beavers, W. R., and Covino, B. G.: Relationship of potassium and calcium to hypothermic ventricular fibrillation, J. Appl. Physiol. 14: 60, 1959.
34. Beavers, W. R., and Rogers, J. T., Jr.: Hypothermia: alterations in cardiac and skeletal muscle electrolytes, Am. J. Physiol. 196: 706, 1959.
35. Behnke, A. R., and Yaglou, C. P.: Physiological responses of men to chilling in ice water and to slow and fast rewarming, J. Appl. Physiol. 3: 591, 1951.
36. Bering, E. A., Jr., Taren, J. A., McMurray, J. D., and Bernhard, W. F.: Studies on hypothermia in monkeys; effect of hypothermia on the general physiology and cerebral metabolism of monkeys in the hypothermic state, Surg. Gynec & Obst. 102: 134, 1956.
37. Berman, E. J., Taylor, M. T., and Frisch, C.: Experimental prevention of ventricular fibrillation following hypothermia and induced cardiac arrest, J. Thoracic Surg. 35: 483, 1958.
38. Berne, R. M.: Myocardial function in severe hypothermia, Circulation Res. 2: 90, 1954.

39. Berne, R. M.: Effect of immersion hypothermia on coronary blood flow, Circulation Res. 2: 236, 1954.
40. Bernhard, W. F., McMurrey, J. D., and Curtis, G. W.: Feasibility of partial hepatic resection under hypothermia, New England J. Med. 253: 159, 1955.
41. Bernhard, W. F., McMurrey, J. D., Ganong, W. F., and Lennihan, R.: Effect of hypothermia on peripheral serum levels of free 17-hydroxycorticoids in dog and man, Ann. Surg. 143: 210, 1956.
42. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General hypothermia for experimental intracardiac surgery; use of electrophrenic respirations, artificial pacemaker for cardiac standstill, and radio-frequency rewarming in general hypothermia, Ann. Surg. 132: 531, 1950.
43. Bigelow, W. G., Hopps, J. A., and Callaghan, J. C.: Radio-frequency rewarming in resuscitation from severe hypothermia, Canad. J. M. Sc. 30: 185, 1952.
44. Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F.: Hypothermia: possible role in cardiac surgery; investigation of factors governing survival in dogs at low body temperature, Ann. Surg. 132: 948, 1950.
45. Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F.: Oxygen transport and utilization in dogs at low body temperatures, Am. J. Physiol. 160: 125, 1950.
46. Bigelow, W. C., and McBirnie, J. E.: Further experiences with hypothermia for intracradiac surgery in monkeys and groundhogs, Ann. Surg. 137: 361, 1953.
47. Bigelow, W. G., Mustard, W. T., and Evans, J. G.: Some physiologic concepts of hypothermia and their applications to cardiac surgery, J. Thoracic Surg. 28: 463, 1954.
48. Birkeland, S., Vogt, A., Krog, J., and Semb, C.: Renal circulatory occlusion and local cooling, J. Appl. Physiol. 14: 227, 1959.
49. Blades, B., and Pierpont, H. C.: Simple method of inducing hypothermia, Ann. Surg. 140: 557, 1954.
50. Blair, E., Austin, R. R., Blount, S. G., Jr., and Swan, H.: Study of cardiovascular changes during cooling and rewarming in human subjects undergoing total circulatory occlusion, J. Thoracic Surg. 33: 707, 1957.
51. Blair, E., Montgomery, A. V., and Swan, H.: Posthypothermic circulatory failure; physiologic observations on circulation, Circulation 13: 909, 1956.
52. Blair, E., Swan, H., and Virtue, R.: Clinical hypothermia; study of ice-water surface immersion and short-wave diathermy rewarming technics, Am. Surgeon 22: 869, 1956.
53. Blair, E., Zimmer, R., and Martin, L.: Hemodynamic effects of total circulatory occlusion during hypothermia, Surg. Gynec. & Obst. 108: 13, 1959.
54. Blake, H. A., Goyette, E. M., Lyter, C. S. and Swan, H.: Subcutaneous fat necrosis complicating hypothermia, J. Pediat. 46: 78, 1955.
55. Boatman, K. K., and Bradford, V. A.: Excision of internal carotid aneurysm during pregnancy employing hypothermia and a vascular shunt, Ann. Surg. 148: 271, 1958.
56. Boba, A.: Abnormal electrocardiographic pattern and its relation to ventricular fibrillation; observations during clinical and experimental hypothermia, Am. Heart J. 57: 255, 1959.
57. Boere, L. A.: Ventricular fibrillation in hypothermia, Anaesthesia 12: 299, 1957.
58. Bohm, E., Gordon, E.: Tovi, D. Persson, P. O.: New device for induced hypothermia in intracranial surgery; preliminary report, Acta chir. scandinav. 113: 1, 1957.
59. Botterell, E. H., Lougheed, W. M., Morley, T. P., and Vandewater, S. L.: Hypothermia in surgical treatment of ruptured intracranial aneurysms, J. Neurosurg. 15: 4, 1958.
60. Botterell, E. H., Lougheed, W. M., Scott, J. W., and Vandewater, S. L.: Hypothermia and interruption of carotid, or carotid and vertebral circulation in surgical management of intracranial aneurysms, J. Neurosurg. 13: 1, 1956.
61. Bourgeois-Gavardin, M., Fabian, L. W., Sealy, W. C., Brown, I. W., Jr., and Stephen, C. R.: Management of anesthesia and hypothermia for open heart surgery with extracorporeal circulation, Anesth. & Analg. 37: 197, 1958.
62. Boyd, W. M.: Hypothermia in hyperthyroidism; case report, Am. Surgeon 22: 857, 1956.
63. Brauer, R. W., Leong, C. F., and Holloway, R. J.: Mechanics of bile secretion: effect of perfusion pressure and temperature on bile flow and bile secretion pressure, Am. J. Physiol. 177: 103, 1954.
64. Brayton, D., and Lewis, G. B.: Use of hypothermia in general pediatric surgery, Ann. Surg. 145: 304, 1957.
65. Brewer, L. A., and King, E. L.: Hypothermia in thoracic and thoracoabdominal surgery; use of light cooling as adjunct to anesthesia in poor risk patients, Am. J. Surg. 96: 137, 1958.
66. Brewin, E. G.: Defibrillation of ventricles in hypothermia, Lancet 2: 369, 1954.
67. Brewin, E. G., Gould, R. P., Nashat, F. S. and Neil, E.: Investigation of problems of acid-base equilibrium in hypothermia, Guy's Hosp. Rep. 104: 177, 1955.
68. Brewin, E. G., Nashat, F. S., and Neil, E.: Acid-base equilibrium in hypothermia, Brit. J. Anaesth. 28: 2, 1956.
69. Brock, R.: Hypothermia and open cardiotomy, Proc. Roy. Soc. Med. 49: 347, 1956.

70. Brock, R., and Ross, D. N.: Hypothermia: clinical application of hypothermic techniques: arteriovenous cooling, Guy's Hosp. Rep. 104: 99, 1955.
71. Brockman, S. K., and Fonkalsrud, E.: Experimental open heart surgery employing hypothermia, mecholyl arrest, and carotid perfusion, Surgery 43: 815, 1958.
72. Bromberger-Barnea, B., Caldini, P., and Wittenstein, G. J.: Transmembrane potentials of normal and hypothermic human heart, Circulation Res. 7: 138, 1959.
73. Brooks, C. Mc., and Hoffman, B. F.: in Dripps, R. D.: The Physiology of Induced Hypothermia. Washington, D. C., National Academy of Sciences-National Research Council, publication 451, 1956, p. 362.
74. Brown, D. E. S.: in Dripps, R. D.: The Physiology of Induced Hypothermia. Washington, D. C., National Academy of Sciences-National Research Council, Publication 451, 1956, pp. 3–4.
75. Brown, I. W., Jr., Smith, W. W., and Emmons, W. O.: Efficient blood heat exchanger for use with extracorporeal circulation, Surgery 44: 372, 1958.
76. 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. Thoracic Surg. 36: 497, 1958.
77. Brown, W. E. L., and Hill, A. V.: Oxygen dissociation curve of blood: its thermodynamic basis, Proc. Roy. Soc. (series B) 94: 297, 1923.
78. Bullard, R. W.: Cardiac output of hypothermic rat, Am. J. Physiol. 196: 415, 1959.
79. Bunker, J. P., and Goldstein, R.: Coagulation during hypothermia in man, Proc. Soc. Exper. Biol. & Med. 97: 199, 1958.
80. Burch, B. H., Traphagen, D. W., Folkman, M. J., Rosenbaum, D. A., and Mueller, E. G.: Temporary aortic occlusion in abdominal surgery, Surgery 35: 684, 1954.
81. Burrows, M. Mc., Dundee, J. W., Francis, I. L., Lipton, S., and Sedzimir, C. B.: Hypothermia for neurological operations, Anaesthesia 11: 4, 1956.
82. Caldini, P., and Bromberger-Barnea, B.: Effects of magnesium and tetraethyl-ammonium chloride on hypothermic heart, Science 128: 1435, 1958.
83. Callaghan, J. C., McQueen, D. A., Scott, J. W., and Bigelow, W. G.: Cerebral effects of experimental hypothermia, A. M. A. Arch. Surg. 68: 208, 1954.
84. Caranna, L. J., Telmosse, F. J., and Swan, H.: Effect of intravenous nutrient solutions on ventricular fibrillation in hypothermic dog, A. M. A. Arch. Surg. 76: 394, 1958.
85. Cardi, L.: Functional changes of heart during hypothermia; electrocardiographic and phonocardiographic study, Angiology 7: 171, 1956.
86. Chalmers, P. H., Radcliffe, G. J., and Hardy, T. C.: Anesthetic management in more than 500 aortic operations, Anesth. & Analg. 36: 19, 1957.
87. Chatfield, P. O., Battista, A. F., Lyman, C. P., and Garcia, J. P.: Effects of cooling on nerve conduction in hibernator and non-hibernator, Am. J. Physiol. 155: 179, 1948.
88. Chin, E. F., and Ross, D. N.: Myxoma of left atrium; successful surgical removal under hypothermia, Brit. M. J. 1: 1447, 1957.
89. Choh, L. L.: Effect of cooling on neuromuscular transmission in rat, Am. J. Physiol. 194: 200, 1958.
90. Churchill-Davidson, H. C., McMillan, I. K. R., Melrose, D. G., and Lynn, R. B.: Hypothermia; experimental study of surface cooling, Lancet 2: 1011, 1953.
91. Ciocatto, E., and Cattaneo, A. D.: Experimental and clinical results with controlled hypothermia, ANESTHESIOLOGY 17: 16, 1956.
92. Clark, L. C., Jr., and Trolander, H.: Thermometer for measuring body temperature in hypothermia, J. A. M. A. 155: 251, 1954.
93. Claus, R. H., Junker, R. D., Browning, L. D., and MacFee, W. F.: Hypothermia for portacaval shunt, Ann. Surg. 150: 99, 1959.
94. Clutton-Brock, J.: Some details of technique for hypothermia, Brit. J. Anaesth. 31: 210, 1959.
95. Cohen, D., and Hercus, V.: Controlled hypothermia in infants and children, Brit. M. J. 1: 1435, 1959.
96. Collins, H. A., Stahlman, M., and Scott, H. W., Jr.: Occurrence of subcutaneous fat necrosis in infant following induced hypothermia used as adjuvant in cardiac surgery, Ann. Surg. 138: 880, 1953.
97. Connolly, J. E., Samson, P. C., Richards, V., Bruns, D. L., and Cohn, R. B.: Direct vision surgery of acquired aortic and mitral valvular stenosis under hypothermia, Surgery 45: 181, 1959.
98. Cookson, B. A., and Costas-Durieux, J.: Use of arterial transfusion as adjunct to hypothermia in repair of septal defects, Ann. Surg. 140: 100, 1954.
99. Cookson, B. A., and DiPalma, J. R.: Severe bradycardia of profound hypothermia in dog, Am. J. Physiol. 182: 447, 1955.
100. Cooper, K. E., and Kenyon, J. R.: Comparison of temperatures measured in rectum, oesophagus and on surface of aorta during hypothermia in man, Brit. J. Surg. 44: 616, 1957.
101. Couves, C. M.: Overton, R. C., Jr., and Eaton, W. L.: Hematologic changes in hypothermic dogs, Surg. Forum 6: 102, 1956.
102. Covino, B. G.: Antifibrillary effect of mephentermine sulfate (Wyamine) in general hy-

pothermia, J. Pharmacol. & Exper. Therap. 122: 418, 1958.

103. Covino, B. G., and Beavers, W. R.: Effect of hypothermia on ventricular fibrillary threshold, Proc. Soc. Exper. Biol. & Med. 95: 631, 1957.

104. Covino, B. G., and Beavers, W. R.: Changes in cardiac contractility during immersion hypothermia, Am. J. Physiol. 195: 433, 1958.

105. Covino, B. G., and Hegnauer, A. H.: Ventricular excitability during hypothermia and rewarming in dog, Proc. Soc. Exper. Biol. & Med. 89: 659, 1955.

106. Covino, B. G., and Hegnauer, A. H.: Electrolytes and pH changes in relation to hypothermic ventricular fibrillation, Circulation Res. 3: 575, 1955.

107. Covino, B. G., and Hegnaeur, A. H.: Hypothermic ventricular fibrillation and its control, Surgery 40: 475, 1956.

108. Covino, B. G., and Williams, L.: Excitability cycle of ventricle in hypothermia, Am. J. Physiol. 181: 362, 1955.

109. Covino, B. G., Wright, R., and Charleson, A. D.: Effectiveness of several antifibrillary drugs in hypothermic dog, Am. J. Physiol. 181: 54, 1955.

110. Cranston, W. I., Pepper, M. C., and Ross, D. N.: Carbon dioxide and control of respiration during hypothermia, J. Physiol. 127: 380, 1955.

111. Cross, F. S., Jones, R. D., and Berne, R. M.: Localized cardiac hypothermia as adjunct to elective cardiac arrest, Surg. Forum 8: 355, 1958.

112. daCosta, I. A., Ratcliffe, J. W., and Gerbode, F.: Studies on Physiological effects of hypothermia in chronic experimental cyanosis, Ann. Surg. 140: 821, 1954.

113. D'Amato, H. E.: Thiocyanate space and distribution of water in musculature of hypothermic dog, Am. J. Physiol. 178: 143, 1954.

114. D'Amato, H. E., and Hegnauer, A. H.: Blood volume in hypothermic dog, Am. J. Physiol. 173: 100, 1953.

115. Davis, C. H., Jr., and Alexander, E., Jr.: Intracranial aneurysms: evaluation of methods of treatment, South. M. J. 52: 357, 1959.

116. Davis, H. C., Morse, I. S., and Dick, M. M.: Effect of pronestyl on experimental coronary occlusion in hypothermic dogs, Am. J. Surg. 93: 453, 1957.

117. DeBakey, M. E., and Cooley, D. A.: Successful resection of aneurysm of distal aortic arch and replacement by graft, J. A. M. A. 155: 1398, 1954.

118. DeLorme, E. J.: Experimental cooling of blood stream; preliminary communication, Lancet 2: 914, 1952.

119. Deterling, R. A., Nelson, E., Bhonslay, S., and Howland, W.: Study of basic physiologic changes associated with hypothermia, A. M. A. Arch. Surg. 70: 87, 1955.

120. Dewesse, J. A., Jones, T. I., and Mahoney, E. B.: Myocardial metabolism during hypothermia with caval occlusion and low coronary flow, Surg. Forum 7: 298, 1957.

121. Dill, D. B., and Forbes, W. H.: Respiratory and metabolic effects of hypothermia, Am. J. Physiol. 132: 685, 1941.

122. Downing, D. F., Cookson, B. A., Keown, K. K., and Bailey, C. P.: Hypothermia in cardiac surgery, J. Pediat. 44: 134, 1954.

123. Drew, C. E., and Anderson, I. M.: Profound hypothermia in cardiac surgery, Lancet 1: 748, 1959.

124. Drew, C. E., Keen, G., and Benazon, D. B.: Profound hypothermia, Lancet 1: 745, 1959.

125. Dundee, J. W., Francis, I. L., and Sedzimir, C. B.: Safer hypotension, Lancet 1: 885, 1954.

126. Dundee, J. W., Mesham, P. R., and Scott, W. E. B.: Chlorpromazine and production of hypothermia, Anaesthesia, 9: 296, 1954.

127. Dundee, J. W., Scott, W. E. B., and Mesham, P. R.: Production of hypothermia, Brit. M. J. 2: 1244, 1953.

128. Eastcott, H. H. G., Pickering, G. W., and Rob, C. G.: Reconstruction of internal carotid artery in patient with intermittent attacks of hemiplegia, Lancet 2: 994, 1954.

129. Eccleston, H. N., Jr., Coakley, C. S., Alpert, S., and Albert, S. N.: Preliminary report on combination of hypothermic and hypotensive techniques, Anesth. & Analg. 35: 285, 1956.

130. Edmark, K. W.: Prevention of ventricular fibrillation during hypothermia by adjustment of blood pH, 1959 Biennial Western Conference on Anesthesiology, Los Angeles, California, Hollywood Convention Reporting Company, 1959, p. 77.

131. Edwards, G. E.: Use of hypothermia in case of measles meningo-encephalitis, J. Irish M. A. 42: 181, 1958.

132. Edwards, W. S., Simmons, E., Lombardo, C. R., Bennett, A., and Bing, R. J.: Coronary blood flow in hypothermia: incidence of ventricular fibrillation with decreased and increased flow, A. M. A. Arch. Surg. 71: 853, 1955.

133. Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A., and Bing, R. J.: Coronary blood flow and myocardial metabolism in hypothermia, Ann. Surg. 139: 275, 1954.

134. Egdahl, R. H., Nelson, D. H., and Hume, D. M.: Adrenal cortical function in hypothermia, Surg. Gynec. & Obst. 101: 715, 1955.

135. Ehrmantraut, W. R., Ticktin, H. E., and Fazekas, J. F.: Cerebral hemodynamics and metabolism in accidental hypothermia, A. M. A. Arch. Int. Med. 99: 57, 1957.

136. Eiseman, B., Malette, W. G., Wotkyns, R. S., Summers, W. B., and Tong, J. L.: Pro-

longed hypothermia in experimental pneumococcal peritonitis, J. Clin. Invest. 35: 940, 1956.
137. Eiseman, B., Owens, J. C., and Swan, H.: Hypothermia in general surgery, New England J. Med. 255: 750, 1956.
138. Elliott, H. W., and Crismon, J. M.: Increased sensitivity of hypothermic rats to injected potassium and influence of calcium, digitalis, and glucose on survival, Am. J. Physiol. 151: 366, 1947.
139. Ellis, P. R., Jr., Kleinsasser, L. J., and Speer, R. J.: Changes in coagulation occurring in dogs during hypothermia and cardiac surgery, Surgery 41: 198, 1957.
140. Emslie-Smith, D.: Spatial vectorcardiogram in hypothermia, Brit. Heart J. 20: 175, 1958.
141. Emslie-Smith, D.: Accidental hypothermia; common condition with pathognomonic electrocardiogram, Lancet 2: 492, 1958.
142. Fabian, L. W., Stainton, R., Hara, M., Ling, P. C., and Shafer, C. W.: Chemophysiologic alterations during hypothermia, ganglioplegia and intracardiac surgery, Anesth. & Analg. 34: 214, 1955.
143. Fairfield, J.: Effects of cold on infant rats: body temperatures, oxygen consumption, electrocardiograms, Am. J. Physiol. 155: 355, 1948.
144. Fairley, H. B.: Hypothermia for adult cardiovascular surgery: technique of anaesthesia, Canad. Anaesth. Soc. J. 4: 96, 1957.
145. Fairley, H. B., Waddell, W. C., and Bigelow, W. G.: Hypothermia for cardiovascular surgery; acidosis in rewarming period, Brit. J. Anaesth. 29: 310, 1957.
146. Fay, T.: Early experiences with local and generalized refrigeration of human brain, J. Neurosurg. 16: 239, 1959.
147. Fay, T., and Smith, G. W.: Observations of reflex responses during prolonged periods of human refrigeration, A. M. A. Arch. Neurol. & Psychiat. 45: 215, 1941.
148. Fedor, E. J., and Fisher, B.: Simultaneous determination of blood volume with Cr^{51} and T-1824 during hypothermia and rewarming, Am. J. Physiol. 196: 703, 1959.
149. Fedor, E. J., Fisher, B., and Lee, S. H.: Rewarming following hypothermia of two to twelve hours; cardiovascular effects, Ann. Surg. 147: 515, 1958.
150. Fedor, E. J., Levine, M., Russ, C., and Fisher, B.: Effect of prolonged hypothermia on oxygen consumption of liver slice, Surg. Forum 6: 506, 1956.
151. Ferguson, A. T., Wilson, J. N., Jenkins, D., and Swan, H.: Effect of hypothermia on hemorrhagic shock, Ann. Surg. 147: 281, 1958.
152. Fisher, E. R., Fedor, E. J., and Fisher, B.: Stressor effect of hypothermia in the rat, Am. J. Physiol. 188: 470, 1957.
153. Fisher, E. R., Fedor, E. J., and Fisher, B.: Pathologic and histochemical observations in experimental hypothermia, A. M. A. Arch. Surg. 75: 817, 1957.
154. Fisher, B., Fedor, E. J., and Lee, S. H.: Rewarming following hypothermia of two to twelve hours; some metabolic effects, Ann. Surg. 148: 32, 1958.
155. Fisher, B., Fedor, E. J., Lee, S. H., Weitzel, W. K., Selker, R., and Russ, C.: Some physiologic effects of short- and long-term hypothermia upon liver, Surgery 40: 862, 1956.
156. Fisher, B., Russ, C., and Fedor, E. J.: Effect of hypothermia of 2 to 24 hours on oxygen consumption and cardiac output in dog, Am. J. Physiol. 188: 473, 1957.
157. Fisher, B., Russ, C., Fedor, E., Wilde, R., Engstrom, P., Happel, J., and Pendergast, P.: Experimental evaluation of prolonged hypothermia, A. M. A. Arch. Surg. 71: 431, 1955.
158. Fleming, P. R., and Muir, F. H.: Electrocardiographic changes in induced hypothermia in man, Brit. Heart J. 19: 59, 1957.
159. Fleming, R.: Acid-base balance of blood in dogs at reduced body temperature, A. M. A. Arch. Surg. 68: 145, 1954.
160. Forrester, A. C.: Hypothermia using air cooling, Anaesthestia 13: 289, 1958.
161. Frank, H. A., and Carr, M. H.: Adaptive changes in hypothermia with special reference to electrolyte alterations; experimental study, West. J. Surg. 66: 105, 1958.
162. Fuhrman, F. A., and Crismon, J. M.: Influence of acute hypothermia on rate of oxygen consumption and glycogen content liver and on blood glucose, Am. J. Physiol. 149: 552, 1947.
163. Ganong, W. F., Bernhard, W. F., and Murrey, J. D.: Effect of hypothermia on output of 17-hydroxycorticoids from adrenal vein in dog, Surgery 38: 506, 1955.
164. Garb, S., and Scriabine, A.: Relationship of temperature to utilization of glucose for contractile force by cat heart muscle, Am. J. Physiol. 180: 101, 1955.
165. Gardner, W. J., Wasmuth, C. E., and Hale, D. E.: Method of converting operating table into refrigerating trough, J. Neurosurg. 13: 122, 1956.
166. Gerbode, F., daCosta, I. A., and Ratcliffe, W.: Liver circulation in general hypothermia; effect of cooling upon oxygen saturation and electrolytes in hepatic blood, Stanford M. Bull. 14: 57, 1956.
167. Goldberg, L. J.: Effects of hypothermia on contractility of intact dog heart, Am. Physiol. 194: 92, 1958.
168. Gollan, F.: Cardiac arrest of one hour duration in dogs during hypothermia of 0° followed by survival, Fed. Proc. 13: 57, 1954.

169. Gollan, F., Blos, P., and Schuman, H.: Studies on hypothermia by means of pump-oxygenator, Am. J. Physiol. 171: 331, 1952.
170. Gollan, F., Grace, J. T., Schell, M. W., Tysinger, D. S., and Feaster, L. B.: Left heart surgery in dogs during respiratory and cardiac arrest at body temperatures below 10 C., Surgery 38: 363, 1955.
171. Gollan, F., Hamilton, E. C., and Meneely, G. R.: Consecutive survival of open-chest, hypothermic dogs after prolonged by-pass of heart and lungs by means of pump-oxygenator, Surgery 35: 88, 1954.
172. Gollan, F., and Nelson, I. A.: Anoxic tolerance of beating and resting heart during perfusion at various temperatures, Proc. Soc. Exper. Biol. & Med. 95: 485, 1957.
173. 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.
174. Goodall, R. G. W., Hyndman, W. W. B., and Guard, F. N.: Studies on hypothermia in abdominal surgery; occlusion of vascular inflow to liver, A. M. A. Arch. Surg. 75: 1011, 1957.
175. Gray, T. C.: Discussion on induced hypothermia, Proc. Roy. Soc. Med. 48: 1083, 1955.
176. Grosskreutz, D. C., Magee, A. C., and Stephen, C. R.: Value of hypothermia during aortic occlusion, J. A. M. A. 165: 949, 1957.
177. Grow, J. B., Demong, C. V., and Hawes, C. R.: Surgical treatment of ventricular septal defects: method utilizing selective coronary perfusion and hypothermia, J. Thoracic Surg. 32: 669, 1956.
178. Grumbach, L., Howard, J. W., and Merrill, V. L.: Factors related to initiation of ventricular fibrillation in isolated heart: effect of calcium and potassium, Circulation Res. 2: 452, 1954.
179. Gubler, E. V.: Anesthesia by hypothermia in animals, Anesth. & Analg. 37: 398, 1958.
180. Gunton, R. W., Scott, J. W., Lougheed, W. M., and Botterell, E. H.: Changes in cardiac rhythm and in form of electrocardiogram resulting from induced hypothermia in man, Am. Heart J. 52: 419, 1956.
181. Gwathmey, O., and Pierpont, H. C.: Stage occlusion and resection of human aortic arch with hypothermia, Am. Surgeon 21: 827, 1955.
182. Hallet, E. B.: Effect of decreased body temperature on liver function and splanchnic blood flow in dogs, Surg. Forum 5: 362, 1955.
183. Hamilton, J. B., Dresbach, M., and Hamilton, R. S.: Cardiac changes during progressive hypothermia, Am. J. Physiol. 118: 71, 1937.
184. Hannon, J. P.: Effect of temperature on heart rate, electrocardiogram and certain myocardial oxidations of rat, Circulation Res. 6: 771, 1958.
185. Hara, M., Harberg, F. J., and Hudson, L. H.: Antifibrillatory action of piperidolate hydrochloride (Dactil) in hypothermia, A. M. A. Arch. Surg. 75: 780, 1957.
186. Hardin, C. A., Reismann, K. R., and Dimond, E. G.: Use of hypothermia in resection and homologous graft replacement of thoracic aorta, Ann. Surg. 140: 720, 1954.
187. Hardin, C. A., and Valk, W. L.: Effect of temporary ischemia on renal function under normal and hypothermic temperatures with aortic renal graft replacement, Surg. Gynec. & Obst. 106: 82, 1958.
188. Hebert, C. L., and Merzig, J. E.: Inflatable tub for hypothermia, ANESTHESIOLOGY 19: 287, 1958.
189. Hebert, C. L., Severinghaus, J. W., and Radigan, L. R.: Management of patients during hypothermia, Anesth. & Analg. 36: 24, 1957.
190. Hegnauer, A. H., and D'Amato, H. E.: Oxygen consumption and cardiac output in hypothermic dog, Am. J. Physiol. 178: 138, 1954.
191. Hegnauer, A. H., D'Amato, H., and Flynn, J.: Influence of intraventricular catheter on course of immersion hypothermia in dogs, Am. J. Physiol. 167: 63, 1951.
192. Hegnauer, A. H., Flynn, J., and D'Amato, H.: Cardiac physiology in dog during rewarming from deep hypothermia, Am. J. Physiol. 167: 69, 1951.
193. Hegnauer, A. H., Schriber, W. J., and Harterius, H. O.: Cardiovascular response of the dog to immersion hypothermia, Am. J. Physiol. 161: 455, 1950.
194. Hellings, P. M.: Controlled hypothermia; recent developments in use of hypothermia in neurosurgery, Brit. M. J. 2: 346, 1958.
195. Helmsworth, J. A., and Cole, W. R.: Comparison of two methods of induction of hypothermia in dogs, A. M. A. Arch. Surg. 73: 481, 1956.
196. Helmsworth, J. A., Stiles, W. J., and Elstun, W.: Changes in blood cellular elements in dogs during hypothermia, Surgery 38: 843, 1955.
197. Helmsworth, J. A., Stiles, W. J., and Elstun, W.: Leukopenia and thrombocytopenia effect of hypothermia in dogs, Proc. Soc. Exper. Biol. & Med. 90: 474, 1955.
198. Henneman, D. H., Bunker, J. P., and Brewster, W. R., Jr.: Immediate metabolic response to hypothermia in man, J. Appl. Physiol. 12: 164, 1958.
199. Hercus, V., Cohen, D., and Bowring, A. C.: Temperature gradients during hypothermia, Brit. M. J. 2: 1439, 1959.
200. Hicks, C. E., McCord, M. C., and Blount, S. G., Jr.: Electrocardiographic changes

during hypothermia and circulatory occlusion, Circulation 13: 21, 1956.
201. Hill, D. W.: Measurement and recording of temperatures during hypothermia, Brit. J. Anaesth. 31: 22, 1959.
202. Holswade, G. R., and Engle, M. A.: Collapsible tub for immersion cooling on the operating table, Surg. Gynec. & Obst. 106: 502, 1958.
203. Holt, M. H., Benvenuto, R., and Lewis, F. J.: General hypothermia with intragastric cooling, Surg. Gynec. & Obst. 107: 251, 1958.
204. Hong, S. K.: Renal function during hypothermia and hibernation, Am. J. Physiol. 188: 137, 1957.
205. Hook, W. E., and Stormont, R. T.: Effect of lowered body temperature on heart rate, blood pressure, and electrocardiogram, Am. J. Physiol. 133: 334, 1941.
206. Horvath, S. M., Hutt, B. K., Spurr, G. B., and Stevens, G. E.: Some metabolic responses of dogs having low body temperature, Science 118: 100, 1953.
207. Horvath, S. M., Rubin, A., and Foltz, E. L.: Thermal gradients in vascular system, Am. J. Physiol. 161: 316, 1954.
208. Howell, D. A., Stratford, J. G., and Posnikoff, J.: Prolonged hypothermia in treatment of massive cerebral hemorrhage; preliminary report, Canad. M. Ass. J. 75: 388, 1956.
209. Huggins, C. E., and Carter, E. L.: Partial hepatectomy employing differential hypothermia, A. M. A. Arch. Surg. 74: 189, 1957.
210. Huggins, C., Carter, E. L., and McDermott, W. V.: Differential hypothermia in experimental hepatic surgery; application of this technique to problem in clinical surgery, A. M. A. Arch. Surg. 74: 327, 1957.
211. Hunter, A. R.: Chlorpromazine as aid to cooling in thyroid crisis, Lancet 2: 173, 1955.
212. Hyndman, W. W. B., Goodall, R. G. W., and Curd, F. N.: Studies on hypothermia in abdominal surgery; occlusion of abdominal aorta above celiac axis, A. M. A. Arch. Surg. 75: 500, 1957.
213. Inglis, J. M., Biffen, W. H., and d'Abreu, A. L.: Convenient apparatus for providing controlled hypothermia, Lancet 1: 549, 1954.
214. Inglis, J. M., and Turner, E.: Use of hypothermia in non-vascular intracranial tumours, Brit. M. J. 1: 1335, 1957.
215. Itzhaki, S., and Wertheimer, E.: Changes in carbohydrate metabolism of cardiac and striated muscle in hypothermic rats, Circulation Res. 5: 451, 1957.
216. Jackson, D., White, L., and Moyer, J. H.: Hypothermia; study of hypothermia induction time with various pharmacologic agents, Proc. Soc. Exper. Biol. & Med. 100: 332, 1959.
217. Jesati, R. M.: Management of severe hyperthermia with chlorpromazine and refrigeration; report of case, New England J. Med. 254: 426, 1956.
218. Johansson, B., Biorck, G., Haeger, K., and Sjostrom, B.: Electrocardiographic observations on patients operated upon in hypothermia, Acta med. scandinav. 155: 257, 1956.
219. Johnston, A. W., McLean, A. E. M., Morris, R. V., and Ross, E. J.: Hyperpyrexia in encephalitis treated by hypothermia, Lancet 2: 670, 1958.
220. Jude, J. R., Haroutunian, L. M., and Folse, R.: Hypothermic myocardial oxygenation, Am. J. Physiol. 190: 57, 1957.
221. Julian, O. C., Dye, W. S., Grove, W. J., Sadove, M. S., and Coelho, H. M.: Hypothermia in open heart surgery, A. M. A. Arch. Surg. 73: 493, 1956.
222. Julian, O. C., Grove, W. J., Dye, W. S., Sadove, M. S., Javid, H., and Rose, R. F.: Hypotension and hypothermia in surgery of thoracic aorta, A. M. A. Arch. Surg. 70: 729, 1955.
223. Juvenelle, A., Lind, J., and Wegelius, C.: New method of extracorporeal circulation in deep hypothermia combined with artificial circulation, Am. Heart J. 47: 692, 1954.
224. Kajikuri, H., Shumacker, H. B., Jr., and Riberi, A.: Effect of hypothermia and of chlorpromazine on survival after tourniquet shock, Ann. Surg. 146: 799, 1957.
225. Kanter, G. S.: Renal clearance of glucose in hypothermic dogs, Am. J. Physiol. 196: 866, 1959.
226. Kaplan, A., and Fisher, B.: Prevention of fibrillation during hypothermia by pericardial space perfusion, A. M. A. Arch. Surg. 77: 319, 1958.
227. Kaplan, S., Mathews, E. C., Schwab, L., and Clark, L. C., Jr.: Oxygen availability to brain during inflow occlusion of heart in normothermia and hypothermia, J. Thoracic Surg. 32: 576, 1956.
228. Kaufman, N., Gavan, T. L., and Hill, R. W.: Effect of prolonged hypothermia on the rat, A. M. A. Arch. Path. 66: 96, 1958.
229. Kenyon, J. R., and Ludbrook, J.: Hypothermia below 10 C. in dogs with cardiac recovery on rewarming, Lancet 2: 171, 1958.
230. Kenyon, J. R., Ludbrook, J., Downs, A. R., Tait, I. B., Brooks, D. K., and Pryczkowski, J.: Experimental deep hypothermia, Lancet 2: 41, 1959.
231. Keown, K. K., Gilman, R. A., and Bailey, C. P.: Open heart surgery; anesthesia and surgical experiences, J. A. M. A. 165: 781, 1957.
232. Khalil, H. H.: Effect of hypothermia on hypothalamic-pituitary response to stress, Brit. Med. J. 2: 733, 1954.

233. Khalil, H. H.: Hypothermia by internal cooling, Lancet 1: 185, 1957.
234. Khalil, H. H.: Hypothermia by internal cooling in man, Lancet 1: 1092, 1958.
235. Khalil, H. H.: Simple method of raising and lowering body temperature, Brit. M. J. 2: 734, 1954.
236. Kimoto, S., Sugie, S., and Asano, K.: Open heart surgery under direct vision with aid of brain cooling by irrigation, Surgery 39: 592, 1956.
237. Kirby, C. K., Jensen, J. M., and Johnson, J.: Defibrillation of ventricles under hypothermic conditions, A. M. A. Arch. Surg. 68: 663, 1954.
238. Knocker, P.: Effects of experimental hypothermia on vital organs, Lancet 2: 837, 1955.
239. Kortz, A. B.: Ventricular fibrillation during hypothermia: further observations, Am. Surgeon 24: 692, 1958.
240. Kuhn, L. A., and Turner, J. K.: Alterations in pulmonary and peripheral vascular resistance in immersion hypothermia, Circulation Res. 7: 366, 1959.
241. Kyle, R. H., and Kirby, C. K.: Use of potassium chloride for defibrillation of ventricles of hypothermic dog, A. M. A. Arch. Surg. 74: 136, 1957.
242. Lange, K., Weiner, D., and Gold, M. M. A.: Mechanism of cardiac injury in experimental hypothermia, Ann. Int. Med. 31: 989, 1949.
243. Lazorthes, G., and Campan, L.: Hypothermia in treatment of craniocerebral traumatism, J. Neurosurg. 15: 162, 1958.
244. Leblanc, J., and Rosenberg, F.: Effect of dibenamine and pyribenzamine on hypothermia of chlorpromazine, Proc. Exper. Biol. & Med. 97: 95, 1958.
245. Lemmen, L. J., and Davis, J. S.: Studies of cerebrospinal fluid pressure during hypothermia in intracranial surgery, Surg. Gynec. & Obst. 105: 555, 1958.
246. Lemmen, L. J., Davis, J. S., Gigliotti, T. A., and Mulich, E. M.: Study of serum proteins with electrophoresis; observations on serum protein fractions in patients undergoing hypothermia during intracranial surgery, Surg. Gynec. & Obst. 105: 610, 1957.
247. Lewis, F. J.: Hypothermia for open heart surgery, Am. J. Card. 2: 287, 1958.
248. Lewis, F. J., and Niazi, S. A.: Use of carbon dioxide to prevent ventricular fibrillation during intracardiac surgery under hypothermia, Surg. Forum 6: 134, 1956.
249. Lewis, F. J., Ring, D. M., and Alden, J. F.: Technique for total body cooling of febrile, gravely ill patient, Surgery 40: 465, 1956.
250. Lewis, F. J., Shumway, N. E., Niazi, S. A., and Benjamin, R. B.: Aortic valvulotomy under direct vision during hypothermia, J. Thoracic Surg. 32: 481, 1956.
251. Lewis, F. J., and Taufic, M.: Closure of atrial septal defects with aid of hypothermia: experimental accomplishments and report of successful case, Surgery 33: 52, 1953.
252. Lombardo, T. A., Radigan, L. R., and Morrow, A. G.: Myocardial failure in experimental hypothermia, Circulation Res. 5: 22, 1957.
253. Lougheed, W. M., and Kahn, D. S.: Circumvention of anoxia during arrest of cerebral circulation for intracranial surgery, J. Neurosurg. 12: 226, 1955.
254. Lougheed, W. M., Sweet, W. H., White, J. C., and Brewster, W. R.: Use of hypothermia in surgical treatment of cerebral vascular lesions, J. Neurosurg. 12: 240, 1955.
255. Lucas, B. G. B.: Discussion on application of hypothermia to surgical procedures, Proc. Roy. Soc. Med. 49: 345, 1956.
256. Lucas, B. G. B.: Discussion on hypothermia, Proc. Roy. Soc. Med. 50: 76, 1957.
257. Lundberg, N., Nielsen, K. C., and Nilsson, E.: Deep hypothermia in intracranial surgery, J. Neurosurg. 13: 235, 1956.
258. Lynch, H. F., and Adolph, E. F.: Blood flow in small vessels during deep hypothermia, J. Appl. Physiol. 11: 192, 1957.
259. McMurrey, J. D., Bernhard, W. F., Tarentz, J. A., and Bering, E. A.: Studies on hypothermia in monkeys; effect of hypothermia on prolongation of permissible time of total occlusion of afferent circulation of brain, Surg. Gynec. & Obst. 102: 75, 1956.
260. McQuiston, W. O.: Anesthetic problems in cardiac surgery in children, ANESTHESIOLOGY 10: 590, 1949.
261. MacIver, I. N., Lassman, L. P., Thomson, C. W., and McLeod, I.: Treatment of severe head injuries, Lancet 2: 544, 1958.
262. MacPhee, I. W., Gray, T. C., and Davies, S.: Effect of hypothermia on adrenocortical response to operation, Lancet 2: 1196, 1958.
263. Malcolm, J. E., Vernon, F. L. A., Merrifield, A. J., and Beatson, T. R.: Fulminating eclampsia treated by hypothermia, Lancet 1: 863, 1959.
264. Maloney, J. V., Jr., Marable, S., and Longmire, W. P., Jr.: Coronary perfusion as aid to open repair of atrial septal defects under hypothermia, J. Thoracic Surg. 34: 580, 1957.
265. Margolis, R. N.: Physiologic changes in hypothermia and problem of hypothermic ventricular fibrillation, Bull. Tufts-New England Med. Center 4: 151, 1958.
266. Marshall, S. B., Owens, J. C., and Swan, H.: Temporary circulatory occlusion to brain of hypothermic dog, A. M. A. Arch. Surg. 72: 98, 1956.
267. Martin, J. D., Jr., Stone, H. H., and Cooper, F. W., Jr.: Utilization of hypothermia in early burn therapy, Surgery 43: 258, 1958.

268. Martinez, J. B., Kass, I., and Hoffman, M. S.: Factors involved in recovery of patient after prolonged ventricular fibrillation during hypothermia, J. Thoracic Surg. 36: 749, 1958.

269. Mavor, G. E., Harder, R. A., McEvoy, R. K., McCoorn, A. B., and Mahoney, E. B.: Potassium and hypothermic heart, Am. J. Physiol. 185: 515, 1956.

270. Mavor, G. E., McEvoy, R. K., and Mahoney, E. B.: Effectiveness of hypertonic glucose in resuscitation of hypothermic heart following potassium chloride arrest, Circulation Res. 4: 389, 1956.

271. Medins, G., and Laufman, H.: Hypothermia in mesenteric arterial and venous occlusions: experimental study, Ann. Surg. 148: 747, 1958.

272. Melrose, D. G., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective cardiac arrest, Lancet 2: 21, 1955.

273. Meyer, J. S., and Hunter, J.: Effects of hypothermia on local blood flow and metabolism during cerebral ischemia and hypoxia, J. Neurosurg. 14: 210, 1957.

274. Miles, B. E., and Churchill-Davidson, H. C.: Effect of hypothermia on renal circulation of dog, ANESTHESIOLOGY 16: 230, 1955.

275. Miller, J. A., Jr., and Marini, A.: Cardiac activity in apneic five hundred eighty gram human fetus, J. A. M. A. 167: 976, 1958.

276. Miller, J. A., Jr., and Miller, F. S.: Factors in neonatal resistance to anoxia; effects of elevated and reduced temperature upon survival and recovery by neonatal guinea pigs, Surgery 36: 916, 1954.

277. Miorner, G., Haeger, K., and Ryd, H.: Artificial hypothermia in poliomyelitis with hyperpyrexia, Lancet 2: 593, 1955.

278. Montgomery, A. V., Prevedel, A. E., and Swan, H.: Prostigmine (neostigmine) inhibition of ventricular fibrillation in hypothermic dogs, Circulation 10: 721, 1954.

279. Morales, P., Carberry, W., Morello, A., and Morales, G.: Alterations in renal function during hypothermia in man, Ann. Surg. 145: 488, 1957.

280. Morehead, D. E., Lopez-Belio, M., Douglas, G. W., and Julian, O. C.: Comparison of response to potassium cardiac arrest of hearts under hypothermic and normothermic conditions, Surg. Forum 8: 352, 1958.

281. Mortimer, P. L. F.: Surface cooling, new method, Brit. J. Anaesth. 29: 397, 1957.

282. Moulder, P. V., Eichelberger, L., Roma, M., Rams, J. J., Thurston, C., and Pine, R.: Biochemistry of blood, heart, and skeletal muscle under induced, controlled hypothermia, A. M. A. Arch. Surg. 78: 37, 1959.

283. Moulder, P. V., and Thompson, R. G.: Protection of heart under hypothermia with acetylcholine arrest, Proc. Soc. Exper. Biol. & Med. 92: 49, 1956.

284. Moyer, J. H., Greenfield, L., Heider, C., and Handley, C.: Hypothermia; effect of agents which depress sympathetic nervous system on hypothermic induction time and on renal functional alterations due to hypothermia, Ann. Surg. 146: 12, 1957.

285. Moyer, J. H., Heider, C., Morris, G. C., Jr., and Handley, C.: Hypothermia; effect of hypothermia on renal damage resulting from ischemia, Ann. Surg. 146: 152, 1957.

286. Moyer, J. H., Morris, G. C., Jr., and DeBakey, M. E.: Hypothermia; effect on renal hemodynamics and on excretion of water and electrolytes in dog and man, Ann. Surg. 145: 26, 1957.

287. Murphy, J. P., Albert, S. N., Swain, G. M., and Coakley, C. S.: Hypothermia as adjunct to surgery of brain, South. M. J. 48: 1221, 1955.

288. Murray, D. B.: Induced hypothermia for radical operation in carcinoma of cervix uteri, Brit. J. Anaesth. 27: 544, 1955.

289. Murray, D. B., and Bruce, D. F.: Hypothermia in treatment of case of postpartum hemorrhage, Lancet 2: 699, 1955.

290. Navratil, J.: Prevention and treatment of ventricular fibrillation in general hypothermia, Am. Surgeon 22: 436, 1956.

291. Neil, E.: Discussion on hypothermia, Proc. Roy. Soc. Med. 50: 75, 1957.

292. Niazi, S. A., and Lewis, F. J.: Tolerance of adult rats to profound hypothermia and simultaneous cardiac standstill, Surgery 36: 25, 1954.

293. Niazi, S. A., and Lewis, F. J.: Effect of carbon dioxide on ventricular fibrillation and heart block during hypothermia in rats and dogs, Surg. Forum 5: 106, 1955.

294. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in dog, Surg. Gynec. & Obst. 102: 98, 1956.

295. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in monkey with recovery after long periods of cardiac standstill, J. Appl. Physiol. 10: 137, 1957.

296. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in man; report of case, Ann. Surg. 147: 264, 1958.

297. O'Brien, L. J., and Guest, M. M.: Function and reactivation of hypothermic heart after potassium arrest, Am. J. Physiol. 196: 691, 1959.

298. Osborn, J. J.: Experimental hypothermia; respiratory and blood *p*H changes in relation to cardiac function, Am. J. Physiol. 175: 389, 1953.

299. Otis, A. B., and Jude, J.: Effect of body temperature on pulmonary gas exchange, Am. J. Physiol. 188: 335, 1957.

300. Overton, R. C., and DeBakey, M. E.: Experimental observations on influence of hypothermia and autonomic blocking agents on hemorrhagic shock, Ann. Surg. 143: 439, 1956.

301. Overton, R. C., Hedge, R., McMurrey, J. D., and DeBakey, M. E.: Blood volume studies in experimental hemorrhagic shock treated by hypothermia and chlorpromazine, Am. Surgeon 24: 978, 1958.

302. Page, L. B.: Effects of hypothermia on renal function, Am. J. Physiol. 181: 171, 1955.

303. Parkhouse, J.: General anaesthesia as aid to therapeutic hypothermia, Brit. M. J. 2: 751, 1957.

304. Parkins, W. M., Ben, M., and Vars, H. M.: Tolerance of temporary occlusion of thoracic aorta in normothermic and hypothermic dogs, Surgery 38: 38, 1955.

305. Parkins, W. M., Jensen, J. M., and Vars, H. M.: Brain cooling in prevention of brain damage during periods of circulatory occlusion in dogs, Ann. Surg. 140: 284, 1954.

306. Pearcy, W. C., and Virtue, R. W.: Electroencephalogram in hypothermia with circulatory arrest, ANESTHESIOLOGY 20: 341, 1959.

307. Peirce, E. C., II, Dabbs, C. H., Rogers, W. K., Rawson, F. L., and Tompkins, R.: Reduced metabolism by means of hypothermia and low flow pump oxygenator, Surg. Gynec. & Obst. 107: 339, 1958.

308. Peirce, E. C., II, and Polley, V. B.: Differential hypothermia for intracardiac surgery; preliminary report of pump-oxygenator incorporating heat exchanger, A. M. A. Arch. Surg. 67: 521, 1953.

309. Penrod, K. E.: Oxygen consumption and cooling rates in immersion hypothermia in dog, Am. J. Physiol. 157: 436, 1949.

310. Penrod, K. E.: Cardiac oxygenation during severe hypothermia in dog, Am. J. Physiol. 164: 79, 1951.

311. Phibbs, C. M., Levy, L. M., and MacLean, L. D.: Influence of temperature and coronary occlusion on ventricular fibrillation threshold, Surg. Gynec. & Obst. 109: 216, 1959.

312. Pierpont, H. C., and Blades, B.: Intrathoracic method for hypothermia; follow-up study, Am. Surgeon 21: 739, 1955.

313. Platner, W. S., and Hosko, M. J.: Mobility of serum magnesium in hypothermia, Am. J. Physiol. 174: 273, 1953.

314. Pontius, R. G., Brockman, H. L., Hardy, E. C., Cooley, D. A. and DeBakey, M. E.: Use of hypothermia in prevention of paraplegia following temporary aortic occlusion: experimental observations, Surgery 36: 33, 1954.

315. Pool, J. L., and Kessler, L. A.: Mechanism and control of centrally induced cardiac irregularities during hypothermia; clinical observations, J. Neurosurg. 15: 52, 1958.

316. Postel, A. H., Reid, L. C., and Hinton, J. W.: Effect of hypothermia in irreversible shock, Circulation Res. 4: 594, 1956.

317. Postel, A. H., Reid, L. C., and Hinton, J. W.: Therapeutic effect of hypothermia in experimental hemorrhagic shock, Ann. Surg. 145: 211, 1957.

318. Prec, O., Rosenman, R., Braun, K., Rodbard, S., and Katz, L. N.: Cardiovascular effects of acutely induced hypothermia, J. Clin. Invest. 28: 293, 1949.

319. Prevedel, A. E., Montgomery, V., and Swan, H.: Effect of coronary perfusion of prostigmine on ventricular fibrillation in hypothermic dog, Proc. Soc. Exper. Biol. & Med. 85: 596, 1954.

320. Purpura, D. P., Pool, J. L., Housepain, E. M., Girado, M., Jacobson, S. A., and Seymour, R. J.: Hypothermic potentiation of centrally induced cardiac irregularities, ANESTHESIOLOGY 19: 27, 1958.

321. Radigan, L. R., Lombardo, T. A., and Morrow, A. G.: Prevention of ventricular fibrillation in experimental hypothermia; procaine infiltration of superior atrio-caval junction, Surgery 40: 471, 1956.

322. Radigan, L. R., Lombardo, T. A., and Morrow, A. G.: Myocardial failure in experimental hypothermia, Surg. Forum 6: 137, 1956.

323. Raffucci, F. L., Lewis, F. J., and Wangensteen, O. H.: Hypothermia in experimental hepatic surgery, Proc. Soc. Exper. Biol. & Med. 83: 639, 1953.

324. Rand, R. W.: Hypothermia anesthesia in sitting position; report of two cases of acoustic neurinoma, J. Neurosurg. 14: 648, 1957.

325. Reeves, M. M., and Lewis, F. J.: Total body cooling in critically ill febrile patients, Surgery 44: 84, 1958.

326. Riberi, A., Grice, P. F., Rodriguez, R., Kajikuri, H., and Shumacker, H. B., Jr.: Prolongation of safe period of venous inflow occlusion in hypothermic state by coronary and carotid artery perfusion with oxygenated blood, J. Thoracic Surg. 32: 399, 1956.

327. Riberi, A., Grice, P. F., and Shumacker, H. B., Jr.: Ventricular fibrillation in hypothermic state; effect of sino-auricular node blockade in preventing ventricular fibrillation at low degrees of body temperature, Am. Surgeon 21: 1084, 1955.

328. Riberi, A., and Kajikuri, H.: Experimental repair of cardiac septal defects; use of hypothermia with coronary and carotid artery perfusion, A. M. A. Arch. Surg. 73: 485, 1956.

329. Riberi, A., Kajikuri, H., and Shumacker, H. B., Jr.: Ventricular fibrillation in hypothermic state; management of coronary air embolism and ventricular fibrillation, A. M. A. Arch. Surg. 72: 502, 1956.

330. Riberi, A., Shumacker, H. B., Jr., Kajikuri, H., Grice, P. F., and Boone, R. D.: Ventricular fibrillation in hypothermic state; general discussion, Surgery 38: 847, 1955.

331. Riberi, A., Siderys, H., and Shumacker, H. B., Jr.: Ventricular fibrillation in hypothermic state; prevention by sino-auricular node blockade, Ann. Surg. 143: 216, 1956.

332. Riley, P. A., Jr., Barila, T. G., and Hughes, C. W.: Ventricular fibrillation in hypothermic dogs as influenced by thiopental, pentobarbital, and succinylcholine, ANESTHESIOLOGY 17: 277, 1956.

333. Riley, P. A., Jr., Barila, T. G., and Hughes, C. W.: Ventricular fibrillation during hypothermia; tolerance of hypothermic dog heart to ventricular fibrillation, A. M. A. Arch. Surg. 73: 985, 1956.

334. Riley, P. A., Jr., Mixon, B. M., Jr., and Barila, T. G.: Antifibrillary drugs for deep hypothermia in dog, Surgery 42: 936, 1957.

335. Rink, R. A., Gray, I., Rueckert, R. R., and Slocum, H. C.: Effect of hypothermia on morphine metabolism in isolated perfused liver, ANESTHESIOLOGY 17: 377, 1956.

336. Ripstein, C. B.: Friedgood, C. E., and Solomon, N.: Technique for production of hypothermia, Surgery 35: 98, 1954.

337. Rodbard, S., Saiki, H., Malin, A., and Young, C.: Significance of changes in plasma and extracellular volumes in induced hyperthermia and hypothermia, Am. J. Physiol. 167: 485, 1951.

338. Roland, S. I.: Hypothermia induced by cystoscopy, J. Urol. 75: 1006, 1956.

339. Rose, J. C., McDermott, T. F., Lilienfield, L. S., Porfido, F. A., and Kelley, R. T.: Cardiovascular function in hypothermic anesthetized man, Circulation 15: 512, 1957.

340. Rosenhain, F. R., and Penrod, K. E.: Blood gas studies in hypothermic dog, Am. J. Physiol. 166: 55, 1951.

341. Rosomoff, H. L.: Hypothermia and cerebral vascular lesions; experimental interruption of middle cerebral artery during hypothermia, J. Neurosurg. 13: 332, 1956.

342. Rosomoff, H. L.: Effects of hypothermia on physiology of nervous system, Surgery 40: 328, 1956.

343. Rosomoff, H. L.: Experimental brain injury during hypothermia, J. Neurosurg. 16: 177, 1959.

344. Rosomoff, H. L., and Gilbert, R.: Brain volume and cerebrospinal fluid pressure, Am. J. Physiol. 183: 19, 1955.

345. Rosomoff, H. L., and Holaday, D. A.: Cerebral blood flow and cerebral oxygen consumption, Am. J. Physiol. 179: 85, 1954.

346. Ross, D. N.: Venous cooling; new method of cooling blood stream, Lancet 1: 1108, 1954.

347. Ross, D. N.: Hypothermia; technique of blood stream cooling, Guy's Hosp. Rep. 103: 97, 1954.

348. Ross, D. N.: Hypothermia; physiologic observations during hypothermia, Guy's Hosp. Rep. 103: 116, 1954.

349. Ross, D. N.: Hypothermia as aid to surgery, Brit. J. Surg. 43: 569, 1956.

350. Ross, D. N.: Discussion on hypothermia, Proc. Roy. Soc. Med. 50: 76, 1957.

351. Rowbotham, G. F., Bell, K., Akenhead, J. and Cairns, A.: Serious head injury in pregnant woman treated by hypothermia, Lancet 1: 1016, 1957.

352. Ruhe, C. H. W., and Horn, R. H.: Circulatory and respiratory effects of hypothermia induced by blood refrigeration, Am. J. Physiol. 182: 325, 1955.

353. Sabiston, D. C., Theilen, E. O., and Gregg, D. E.: Relationship of coronary blood flow and cardiac output and other parameters in hypothermia, Surgery 38: 498, 1955.

354. Salmon, P. A., Griffen, W. O., and Wangensteen, O. H.: Influence of hypothermia on secretory activity of rabbit's appendix and on closed duodenal loops, Proc. Soc. Exper. Biol. & Med., 101: 150, 1959.

355. Sarajas, H. S. S.: Evidence for heart damage in association with systemic hypothermia in dogs, Am. Heart J. 51: 298, 1956.

356. Sarajas, H. S. S., Senning, A., and Kaplan, J.: Heart damage in dogs subjected to hypothermia, circulatory arrest, and cardiac surgery, Am. Heart J. 52: 836, 1956.

357. Schimert, G., and Cowley, R. A.: Defibrillation, cardiac arrest, and resuscitation in deep hypothermia by electrolyte solutions, Surgery 41: 211, 1957.

358. Scott, J. W.: Electroencephalogram during hypothermia, Electroencephal. & Clin. Neurophysiol. 7: 466, 1955.

359. Sealy, W. C., Brown, I. W., Jr., and Young, W. G., Jr.: Report on use of both extracorporeal circulation and hypothermia for open heart surgery, Ann. Surg. 147: 603, 1958.

360. Sealy, W. C., Brown, I. W., Jr., Young, W. G., Jr., Stephen, C. R., Harris, J. S., and Merritt, D.: Hypothermia, low flow extracorporeal circulation and controlled cardiac arrest for open heart surgery, Surg. Gynec. & Obst. 104: 441, 1957.

361. Sealy, W. C., Young, W. G., Jr., Brown, W., Jr., Lesage, A., Callaway, H. A., Jr., Harris, J. S., and Merritt, D.: Potassium, magnesium, and neostigmine for controlled

cardioplegia, A. M. A. Arch. Surg. 77: 33, 1958.

362. Searles, P. W., and Seymour, D. G.: Body temperature: variations and effects during surgery, anesthesia and hypothermia, Anesth. & Analg. 36: 50, 1957.

363. Sedzimir, C. B.: Therapeutic hypothermia in cases of head injury, J. Neurosurg. 16: 407, 1959.

364. Sedzimir, C. B., and Dundee, J. W.: Hypothermia in treatment of cerebral tumours, J. Neurosurg. 15: 199, 1958.

365. Sedzimir, C. B., Jacobs, D., and Dundee, J. W.: Induced hypothermia as therapeutic measure in neurology, Brit. J. Anaesth. 27: 93, 1955.

366. Segar, W. E.: Effect of hypothermia on tubular transport mechanisms, Am. J. Physiol. 195: 91, 1958.

367. Segar, W. E., Riley, P. A., Jr., and Barila, T. G.: Urinary composition during hypothermia, Am. J. Physiol. 185: 528, 1956.

368. Sellick, B. A.: Method of hypothermia for open heart surgery, Lancet 1: 443, 1957.

369. Selman, M. W., and Brofman, B. L.: Effect of hypothermia on survival rates following coronary occlusion in dogs, Surgery 37: 707, 1955.

370. Severinghaus, J. W.: Oxyhemoglobin dissociation curve correction for temperature and pH variation in human blood, J. Appl. Physiol. 12: 485, 1958.

371. Severinghaus, J. W., and Stupfel, M.: Respiratory dead space increase following atropine in man, and atropine, vagal or ganglionic blockade and hypothermia in dogs, J. Appl. Physiol. 8: 81, 1955.

372. Shafer, P. W., Hughes, C. W., and Barila, T. G.: Tolerance of hypothermic normal dog's heart to ventricular fibrillation, A. M. A. Arch. Surg. 70: 723, 1955.

373. Shields, T. W., and Lewis, F. J.: Rapid cooling and surgery at temperatures below 20 C., Surgery 46: 164, 1959.

374. Shumacker, H. B., Jr., Riberi, A., Boone, R. D., and Kajikuri, H.: Ventricular fibrillation in hypothermic state; role of extrinsic cardiac innervation, Ann. Surg. 143: 223, 1956.

375. Shumway, N. E., Gliedman, M. L., and Lewis, F. J.: Coronary perfusion for longer periods of cardiac occlusion under hypothermia, J. Thoracic Surg. 30: 598, 1955.

376. Siems, M. V., Horvath, S. M., Spurr, G. B., Hutt, B. K., and January, L. E.: Electrocardiographic observations in experimental hypothermia in dogs, Am. J. Physiol. 181: 325, 1955.

377. Sircar, P.: Plasma volume, bleeding and clotting time on hypothermic dogs, Proc. Soc. Exper. Biol. & Med. 87: 194, 1954.

378. Smith, G., Lawson, D., and Penhals, B.: Effect of hypothermia on acute coronary occlusion, Brit. J. Surg. 44: 419, 1957.

379. Smith, L. W., and Fay, T.: Observations on human beings with cancer maintained at reduced temperature of 75–90 Fahrenheit, Am. J. Clin. Path. 10: 1, 1940.

380. Smith, R. T.: Electrolyte studies in experimental animals during hypothermia, Am. J. Surg. 92: 228, 1956.

381. Spencer, F. C., Jude, J. R., and Bahnson, H. T.: Use of coronary perfusion and carbon dioxide regulation in intracardiac operations performed under hypothermia, Surgery 42: 76, 1957.

382. Spurr, G. B., and Barlow, G.: Influence of prolonged hypothermia and hyperthermia on myocardial sodium, potassium, and chloride, Circulation Res. 7: 210, 1959.

383. Spurr, G. B., Barlow, G., and Lambert, H.: Influence of prolonged hypothermia and hyperthermia on cardiac response to injected potassium, Am. J. Physiol. 196: 696, 1959.

384. Spurr, G. B., Horvath, S. M., Hamilton, L. H., and Hutt, B. K.: Temperature gradients in hypothermic dog, Am. J. Physiol. 185: 47, 1956.

385. Spurr, G. B., Hutt, B. K., and Horvath, S. M.: Responses of dogs to hypothermia, Am. J. Physiol. 179: 139, 1954.

386. Stevenson, G. C., Collins, W. F., Randt, C. T., and Saurwein, T. D.: Effects of induced hypothermia on subcortical evoked potentials in the cat, Am. J. Physiol. 194: 423, 1958.

387. Stone, H. H., Donnelly, C., and Frobese, A. S.: Effect of lowered body temperature on cerebral hemodynamics and metabolism of man, Surg. Gynec. & Obst. 103: 313, 1956.

388. Stueber, P. J., Jr., Kovacs, S., Koletsky, S., and Persky, L.: Regional hypothermia in acute renal ischemia, J. Urol. 79: 793, 1958.

389. Stupfel, M., and Severinghaus, J. W.: Internal body temperature gradients during anesthesia and hypothermia and effect of vagotomy, J. Appl. Physiol. 9: 380, 1956.

390. Su, C. S., Hardin, R., and King, H.: Use of hypothermia with cardiopulmonary bypass for open-heart surgery; experimental study, Surgery 44: 1079, 1958.

391. Suda, I., Koizumi, K., and Brooks, C. McC.: Analysis of effects of hypothermia on central nervous system responses, Am. J. Physiol. 189: 373, 1957.

392. Swan, H.: Current status of hypothermia, A. M. A. Arch. Surg. 69: 597, 1954.

393. Swan, H.: Pumps or ice? Current status of open intra-cardiac surgery, Rocky Mountain M. J. 55: 40, 1958.

394. Swan, H., and Blount, S. G., Jr.: Visual intracardiac surgery in series of one hundred eleven patients, J. A. M. A. 162: 941, 1956.
395. Swan, H., Blount, S. G., Jr., and Virtue, R. W.: Direct-vision suture of interatrial septal defect during hypothermia, Surgery 38: 858, 1955.
396. Swan, H., Jenkins, D., and Helreich, M. L.: Adrenal cortical response to surgery; changes in plasma and urinary corticosteroid levels during hypothermia in man, Surgery 42: 202, 1957.
397. Swan, H., and Kortz, A. B.: Direct vision trans-aortic approach to aortic valve during hypothermia. Experimental observations and report of successful clinical case, Ann. Surg, 144: 205, 1956.
398. Swan, H., Virtue, R. W., Blount, S. G., Jr., and Kircher, L. T., Jr.: Hypothermia in surgery; analysis of 100 clinical cases, Ann. Surg. 142: 382, 1955.
399. Swan, H., Zeavin, I., Blount, S. G., Jr., and Virtue, R. W.: Surgery by direct vision in open heart during hypothermia, J. A. M. A. 153: 1081, 1953.
400. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V.: Cessation of circulation in general hypothermia; physiologic changes and their control, Ann. Surg. 138: 360, 1953.
401. Talbott, J. H.: Physiologic and therapeutic effects of hypothermia, New England J. Med. 224: 281, 1941.
402. Tentler, R. L., Sadove, M., Becka, D. R., and Taylor, R. C.: Electroencephalographic evidence of cortical death followed by full recovery; protective action of hypothermia, J. A. M. A. 164: 1667, 1957.
403. Vandewater, S. L., Botterell, E. H., and Lougheed, W. M.: Method of anesthesia and hypothermia in cerebral vascular surgery, Canad. Anaesth. Soc. J. 2: 319, 1955.
404. Vandewater, S. L., Lougheed, W. M., Scott, J. W., and Botterell, E. H.: Some observations with use of hypothermia in neurosurgery, Anesth. & Analg. 37: 29, 1958.
405. Vermeulen-Cranch, D. M., and Spierdijk, J.: Temperature controlled cabinet operating table for safe hypothermia, Brit. J. Anaesth. 29: 400, 1957.
406. Villalobos,, T. J., Adelson, E., and Barila, T. G.: Hematologic changes in hypothermic dogs, Proc. Soc. Exper. Biol. & Med. 89: 192, 1955.
407. Villalobos, T. J., Adelson, E., Riley, P. A., and Crosby, W. H.: Cause of thrombocytopenia and leukopenia that occur in dogs during deep hypothermia, J. Clin. Invest. 37: 1, 1958.
408. Virtue, R. W.: Hypothermic Anesthesia, ed. 1. Springfield, Illinois: Charles C Thomas, publisher, 1955, p. 3.
409. Von Kaulla, K. N., and Swan, H.: Clotting deviations in man associated with open heart surgery during hypothermia, J. Thoracic Surg. 36: 857, 1958.
410. Waddell, W. G., Fairley, H. B., and Bigelow, W. G.: Improved management of clinical hypothermia based upon related biochemical studies, Ann. Surg. 145: 542, 1957.
411. Wangensteen, O. H., Root, H. D., Jenson, C. B., Imamoglu, K., and Salmon, P. A.: Depression of gastric secretion and digestion by gastric hypothermia; its clinical use in massive hematemesis, Surgery 44: 265, 1958.
412. Webb, W. R., and Howard, H. S.: Restoration of function of refrigerated heart, Surg. Forum 7: 302, 1957.
413. Wensel, R. H., and Bigelow, W. G.: Use of heparin to minimize thrombocytopenia and bleeding tendency during hypothermia, Surgery 45: 223, 1959.
414. Werner, A. Y., Dawson, D., and Hartenberg, E.: Spontaneous rewarming of hypothermic curarized dog, Science 124: 3232, 1956.
415. Westin, B., Miller, J. A., Jr., Nyberg, R., and Wedenberg, E.: Neonatal asphyxia pallida treated with hypothermia alone or with hypothermia and transfusion of oxygenated blood, Surgery 108: 868, 1959.
416. Williams, G. R., Jr., and Spencer, F. C.: Clinical use of hypothermia following cardiac arrest, Ann. Surg. 148: 462, 1958.
417. Willson, J. T., Miller, W. R., and Eliot, T. S.: Blood studies in hypothermic dog, Surgery 43: 979, 1958.
418. Wilson, J. N., Marshall, S. B., Beresford, V., Montgomery, V., Jenkins, D., and Swan, H.: Experimental hemorrhage: deleterious effect of hypothermia on survival and comparative evaluation of plasma volume changes, Ann. Surg. 144: 696, 1956.
419. Wolff, R. C., and Penrod, K. E.: Factors affecting rate of cooling in immersion hypothermia in dog, Am. J. Physiol. 163: 580, 1950.
420. Woodhall, B., and Reynolds, D. H.: Localized cerebral hypothermia, Proc. Soc. Exper. Biol. & Med. 97: 194, 1958.
421. Woodhall, B., Reynolds, D. H., Mahaley, S. S., Jr., and Sanders, A. P.: Physiologic and pathologic effects of localized cerebral hypothermia, Ann. Surg. 147: 673, 1958.
422. Wotkyns, R. S., Hirose, H., and Eiseman, B.: Prolonged hypothermia in experimental peritonitis; survival of hypothermic animals and effects of combined hypothermia and antibiotics, Surg. Gynec. & Obst. 107: 361, 1958.
423. Wynn, V.: Electrolyte disturbances associated with failure to metabolise glucose during hypothermia, Lancet 2: 575, 1954.

424. Wynn, V.: Metabolism of fructose during hypothermia in man, Clin. Sc. 15: 297, 1956.
425. Young, W. G., Jr., Sealy, W. C., Brown, I. W., Jr., Hewitt, W. C., Jr., Callaway, H. A., Jr., Merritt, D. H., and Harris, J. S.: Method for controlled cardiac arrest as adjunct to open heart surgery, J. Thoracic Surg. 32: 604, 1956.
426. Young, W. G., Jr., Sealy, W. C., Brown, I. W., Jr., Smith, W. W., Callaway, H. A., Jr., and Harris, J. S.: Metabolic and physiologic observations on patients undergoing extracorporeal circulation in conjunction with hypothermia, Surgery 46: 175, 1959.
427. Zaimis, E., Cannard, T. H., and Price, H. L.: Effects of lowered muscle temperature upon neuromuscular blockade in man, Science 128: 34, 1958.
428. Zeavin, I., Virtue, R. W., and Swan, H.: Cessation of circulation in general hypothermia; anesthetic management, ANESTHESIOLOGY 15: 113, 1954.

ELECTROHYSTEROGRAPHY When oxytocin was administered to pregnant patients the electrohysterogram produced was indistinguishable from that of normal labor. When demerol, 100 mg., was administered for analgesia, labor was slowed for one hour and a marked change appeared in the electrical pattern. (*Larks, S. D., and others: Effects of Oxytocic and Analgesic Drugs on Human Electrohysterogram, Obst. & Gynec. 13: 405 (April) 1959.*)

SPHYGMOMANOMETER Arterial blood pressure appears to have been less frequently measured in the first few days after birth than at any other period of life; principally because of the lack of method of measuring the blood pressure, which is sufficiently convenient, accurate and generally accepted. A sphygmomanometer is described which overcomes these difficulties. This apparatus combined the generally accepted Riva-Rocci method with a pulse indicator. Blood pressure is then determined not by auscultation but by return of the radial pulse with deflation of the cuff. Demonstrative blood pressures are presented. (*Ashworth, A. M., Neligan, G. A., and Rogers, J. E.: Sphygmomanometer for Newborn, Lancet 1: 801 (April 18) 1959.*)