CONTROLLED HYPOTHERMIA

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Controlled hypothermia implies a regulated reduction of body temperature within a range compatible with life, as opposed to spontaneous, ungoverned hypothermia arising from accidental exposure to cold. In order to maintain control over body temperature, special care in anaesthetic technique and a knowledge of the altered response to drugs during hypothermia are essential.

When Temple Fay (1938) first proposed the use of total body cooling for malignant disease, he was applying to the whole body a therapeutic principle which had long been used as a local agent. Although lowered body temperature was soon seen to have little influence on the spread of neoplasm, Bigelow *et al.* (1950a) noted that it brought about a reduction in total oxygen requirement of the body. This observation led logically to the deliberate suspension of blood flow for surgical purposes and to the possibility of open or direct vision surgery within the heart chambers (Bigelow *et al.*, 1950b).

During studies on haemorrhagic shock carried out in this laboratory in 1947, it was observed that when the rectal temperature of dogs at low blood pressure levels fell 5-6° C., due to the combined effects of low room temperature, deep anaesthesia and shock, such animals survived for considerably longer periods than did animals kept at similar hypotensive levels in a warm environment. In order to determine whether the suggested relationship between body temperature and resistance to shock could, under certain circumstances, be valid in spite of much previous evidence to the contrary, a more carefully planned experiment was begun in 1950. It was decided, however, not to employ the conventional method of cooling by exposure or immersion, but to utilize a new method whereby heat is extracted from an exteriorized circulation, and in this way to cool the body more uniformly. The difference in physiological response between the two methods was greater than had been anticipated.

The protective influence of hypothermia on survival of tissues and of the intact organism when oxygen transport has been interfered with has now been demonstrated both in the laboratory

(Delorme, 1952) and in the surgical theatre (Lewis and Taufic, 1953; Swan *et al.*, 1953; Cookson *et al.*, 1952). In accordance with Vant Hoff's law, which states that the velocity of chemical reactions increases two to three times with each 10° C. rise in temperature, cellular activity is diminished as cell temperature decreases, with a consequent reduction in oxygen requirement and circulatory needs. It is reasonable, then, to expect a longer survival time when the circulation is suspended locally or centrally during hypothermia. Shock is merely another form of circulatory derangement, and, as it will be shown, develops more slowly and is longer survived under hypothermic conditions. In addition to the oxygen sparing effect of cold, there is a depression of enzyme activity. Autolytic enzyme activation is known to occur readily in the presence of anoxia at normal body temperatures, so that lowered tissue temperatures not only is the onset of anoxia delayed during the failure of oxygen supply, but also retarded are the secondary changes which ordinarily follow upon it and which would result in permanent intracellular disorganization and death. Hypothermia within a reversible range is thus a temporary means of extending the margin of safety for cell vitality in conditions where oxygen distribution is curtailed locally or throughout the general circulation.

Methods

1. Surface cooling.
2. Chemical metabolic depressants.
3. Blood stream cooling:
 - (a) Pervascular.
 - (b) Intragastric.
 - (c) Pulmonary.
 - (d) Intrathoracic.

1. *Surface cooling.* Deriving from the early work of Temple Fay, surface cooling by special refrigerated blankets or by immersion in a bath remains the most commonly used means of inducing hypothermia. This method requires the supervision of a highly skilled anaesthetist in order to control reflex responses to cold, which responses increase both the difficulties of cooling and the

risk of the procedure. Technical details for surface cooling are given by Bigelow *et al.* (1950a).

2. *Chemical methods.* The use of a number of drugs in conjunction with moderate cooling has been advocated by Laborit and Hugenard (1951) with the intention of providing a non-reactive, highly resistant state in surgical patients. This has been further investigated in this country by Dundee *et al.* (1953a and b) and by Churchill-Davidson *et al.* (1953). Largactil (chlorpromazine), which has been identified by Dundee *et al.* to be the most effective of these agents, is being discussed elsewhere in this issue. It is probable that the ideal drug of this type which will act selectively on the temperature control centres has yet to be discovered.

3. *Cooling by way of the circulating blood (pervascular route).* This method was independently developed by Boerema *et al.* (1951) and by Delorme (1952). Improvements have been added by Ross (1954a and b), and an apparatus for blood cooling is now available from a London manufacturer. Details of this equipment have been published by Ross (1954b), but in principle it consists of a cooling coil of siliconed polyvinyl tubing, which is refrigerated throughout its length, by a jacket through which ice-water is constantly circulated. It may be used as an artery-to-vein shunt or as a vein-to-vein perfusion in conjunction with a blood pump. The need for anticoagulants is avoided by the use of cold, smooth, non-wettable surfaces and by ensuring streamlined flow.

A form of indirect blood cooling which also avoids surface stimulation has been reported by Khalil and MacKeith (1954). This consists of circulating ice-water through an intragastric balloon. The method has the advantage of extreme simplicity but it is slow. It may have a special value, however, where more elaborate procedures are impracticable, as in the management of military casualties in the field and during transport. Even less efficient is the method of pulmonary cooling by the use of chilled air or anaesthetic gas. This is not surprising in view of the fact that the thermal conductivity of air is only one-twenty-seventh that of water. Intraperitoneal cooling has been used experimentally in small animals whose vessels are unsuitable for cannulation, and recently Blades and Pierpont (1954) have advocated intrathoracic cooling. They claim that in certain complicated cardiac defects an exact diagnosis may first be made and the need for hypothermia established before cooling is started, which is then carried out by perfusion of the pleural cavity with chilled saline. Immediate access to the heart is also available by this method in the event of ventricular fibrillation or cardiac

arrest. Similar advantages may be obtained if direct blood cooling is begun only after the chest is opened and carried on concurrently with the initial stages of the operation (Brock, 1954).

Arterial cannulation may be avoided by using a vein-to-vein circuit, but the use of a blood pump, which this involves, has certain disadvantages such as red cell and platelet damage. Cell damage is usually not of serious proportions and may be outweighed by the better control of cooling rate and the absence of arterial injury. Repair of the femoral artery after cannulation seldom prevents subsequent thrombosis, although this may later recanalize.

The Physiology of Hypothermia

The most important effects of hypothermia of moderate degree (25° C.) are reduced oxygen requirement and inhibition of enzyme action. There are many other changes which may be conveniently classified into two groups: (1) Those which are beneficial or protective; (2) those which are potentially dangerous.

Beneficial Effects

1. *Reduced oxygen requirement.* In measuring oxygen uptake by Benedict's spirometer, care must be taken that thermal or anaesthetic depression of respiratory activity does not invalidate true oxygen requirement values. If any degree of arterial unsaturation is allowed to occur, oxygen consumption values will be too low. On the other hand, if shivering or other calorogenic responses to cold occur, the oxygen consumption will rise. If these are avoided, however, oxygen consumption at 25° C. falls in a linear fashion with temperature reaching about 25 per cent. of basal values.

2. *Reduced cardiac work* is the result of reduced cardiac rate and output. Only a moderate fall in blood pressure occurs if anaesthesia is light.

3. *Anticoagulant effect.* The anticoagulant effect of cooling is shown by the increase in coagulation time of blood at 25° C. to approximately fifteen minutes. If the blood sample is brought to normal blood temperature, no increase is seen. Thus cooling provides an anti-thrombotic influence which is of value in most surgical procedures, particularly as the actual bleeding time at operation does not seem to be increased.

4. *Reduction in amount of anaesthetic and narcotic agents required.* So marked is this effect in the later phase of cooling that known non-reactive agents such as cyclopropane or nitrous oxide may be preferred to those that must be metabolized or excreted. The anaesthetic action of cold and the fact that the cold reduces the amount of anaesthetic required are frequently referred to,

but it must be noted that (this is not true for the initial stages of cooling if surface cooling is employed. The exact moment when deep anaesthesia necessary for initial cooling must give way to light anaesthesia as lower temperatures are approached is a matter for nice judgment on the part of the anaesthetist, and one in which an error may well have serious consequences. In un-anaesthetised man, somnolence and amnesia occur below 33°C ., with loss of consciousness usually coming on below 28°C . Occasionally children will awaken at even lower temperatures during rewarming. It is possible that deep hypothermia may eventually be used as an independent anaesthetic technique.

5. *Inhibition of enzyme and bacterial activity.* Most enzyme systems have an optimal temperature and are extremely sensitive even to slight deviations from this level. For example, the proteolytic enzymes are only significantly active within a few degrees of normal body temperature. Similarly, bacterial growth is largely suspended at 25°C ., and this may be of importance in preventing overgrowth of anaerobic organisms in ischaemic gut wall, and in liver, at least in the experimental animal. In over 150 thoracotomies performed in dogs under clean but unsterile conditions, no pleural infections occurred. This aspect of cooling is of particular interest in the early management of massive tissue injuries, such as occur in war casualties where large amounts of contaminated, ischaemic muscle may be present.

Effects of Hypothermia which are Potentially Dangerous

1. *Over-response to surface cold.* With exposure to cold there is mobilization of various mechanisms designed to prevent change in body temperature and to maintain homeostasis. Although thyroid activation cannot play any part in the immediate response to cold, the adrenal gland has been shown to undergo marked changes within a matter of two or three hours (Sayers and Sayers, 1949). A drop in eosinophils points to, but does not prove, adrenocortical activation. As the adequate stimulus for shivering is of somatic rather than central origin (Jung *et al.*, 1937), this leads to further oxygen expenditure unless controlled by deep anaesthesia or curariform drugs. There can be a marked rise in metabolism in response to hormonal stimulation, even in the absence of shivering (Dill and Forbes, 1941). It is noteworthy that Dundee *et al.* (1953) found that rises of 20 to 60 per cent. in oxygen consumption occasionally occurred during surface cooling in man in spite of deep anaesthesia and largactil. Even such a moderate rise might well be beyond the tolerance of a patient with a defective cardiovascular system.

In unanaesthetized man exposed to cold this increase in metabolic rate may reach eleven times the basal metabolic rate (Gagge and Herrington, 1947).

2. *Disturbances in cardiac action.* Reversible changes regularly appear in the E.C.G. record, the most important of which are prolonged conduction time and the widening of the Q.R.S. complex. Extra-systoles occasionally occur, and if frequent are considered to be an indication for interrupting or slowing the cooling process. Spontaneous ventricular fibrillation rarely occurs in the absence of cardiac manipulation, but it constitutes a serious danger in all cardiac surgery under hypothermia. Certain drugs, notably prostigmine, have a definite antifibrillatory effect.

3. *Alterations in pH of blood.* The pH of blood tends to be lowered during cooling and this results in undesirable electrolyte and water shifts between cells and the extra-cellular compartment. The loss of potassium from the cell has been associated with increased myocardial irritability and a tendency to ectopic activity (Harris *et al.*, 1954). If moderate hyperventilation is maintained throughout cooling, acid base equilibrium is undisturbed and the above changes are prevented.

4. *Local cold injury.* Although this is theoretically possible in surface cooling, it does not appear to be of practical importance, apart from frost necrosis in infants (Collins *et al.*, 1953). Clinical instances of peripheral vaso-neuropathy have been reported as a result of any form of induced hypothermia.

Cold haemagglutination occurs only below 25°C . and is reversible. The high incidence of this phenomenon during the following attacks of virus pneumonia should be kept in mind. Cold haemolysis, an irreversible condition, occurs between 0 and 5°C . Neither of these complications has been encountered by the author either in animals or in man, during hypothermia.

5. *Metabolic disturbances due to cold.* A reversible inhibition of hepatic and renal function occurs at 25°C . with cessation of bile formation and greatly reduced secretion of urine. Drugs and substances such as glucose, heparin, etc., which are disposed of by inactivation or utilization in liver or by excretion in kidney, tend to accumulate if given during hypothermia and dangerously high blood levels of glucose, for example, have been produced by doses which would be therapeutic at normal body temperature (Wynn, 1954).

6. *'After-drop' in deep temperature.* This is a potentially dangerous fall in central body temperature which occurs after surface cooling has been suspended. It is due to the restoration of circulation through the very cold peripheral tissues. An outer layer of tissue of 2 cm. depth comprises

EXPERIMENTS INVOLVING GENERAL ISCHAEMIA

Nature of Ischaemia	Duration (Minutes)	Average Survival Time at Normal Body Temperature	Result at 25° C.	No of Expts.
B.P. 40 mm.Hg or less	240-300	4 hours (15 dogs)	Full recovery	10
Occlusion of venous return to heart	20-70 (average 32)	6½ minutes	Full recovery	54
Arterial exsanguination B.P.: 0-10 mm. Hg	60-150 (average 83)	5½ minutes	Full recovery	24
Cardiotomy with intracardiac procedures	5-30 (average 13)	—	29 survivals; 12 deaths (irreversible ventricular fibrillation)	41
Chemical arrest of heart action	1-12 (average 8)	—	11 survivals; 9 deaths (irreversible ventricular fibrillation)	20
Chemical arrest plus selective cooling of heart	20-22	—	2 survivals	2

approximately 50 per cent. of the body mass (Edholm, 1954), and the effect of heat equilibration in this large mass with deep body temperature may lead to a sudden drop in deep body temperature of as much as 7° C.

A further danger in unequal cooling is seen in the drop in deep temperature when the chest is opened. This suggests that the internal organs are considerably warmer than the peripheral tissues, and that such organs, which are more susceptible to oxygen lack than peripheral tissues, are less well protected by cold. Simultaneous measurement of temperatures in various parts of the body confirms this gradient during surface cooling. No significant temperature gradient exists during pervascular cooling.

7. In all forms of cooling there is an increase in venous blood volume due to constriction of arterial and capillary vessels by cold. This is shown by (1) slight engorgement of surface veins and (2) liver enlargement and lung congestion which can be demonstrated by X-ray (Glaser *et al.*, 1950). This relative overfilling of the venous system may be an embarrassment to the lungs and to the heart. Great care should be taken in giving excess fluids or blood during hypothermia. Occasionally the removal of a quantity of blood by venesection or interruption of venous return to the heart is indicated by a rising central venous pressure.

Blood viscosity tends to rise steadily with cooling but this may be limited to the physical effect of cold alone by preventing the haematocrit changes already referred to.

Experimental Results

The experiments in which the circulation has been restricted in various ways are summarized in Table I. From this table it can be seen that prolonged haemorrhagic hypotension even to the point of exsanguination is survived at lowered body temperature. Similarly, occlusion of the venous return to the heart can be sustained for as long as 70 minutes. The explanation of the lower mortality and absence of ventricular fibrillation during pervascular cooling may lie in the early cooling of the adrenal gland and the uniformity of cardiac cooling itself. Manipulation of the partially ischaemic, cooled heart produces a considerable mortality from uncontrollable ventricular fibrillation. It may be possible to prevent this or to make it readily reversible by the deliberate arrest of cardiac action during exclusion of blood from the heart cavity. Fig. 1 shows the E.C.G. record of the effect of 8 ml. of 1 : 3,000 prostigmine—a cholinesterase inhibitor—injected into the coronary circulation of a dog's heart at 25° C. with abolition of the effect by atropine (100 mg.), given in the same way. Reversible arrest of the heart has also been achieved by selective cooling of the heart to levels of cold at which all activity ceases (8 to 12° C.), with the rest of the body remaining at 25° C. If a reliable method for inhibiting cardiac action temporarily can be developed, it would enable the surgeon to work within the heart chambers from which both arterial and venous blood has been excluded. When the heart is allowed to continue beating, it requires some degree of coronary flow which must

FIG. 1.—Electrocardiographic record showing inhibition of cardiac activity by prostigmine with abolition of effect by atropine in hypothermic dog.

FIG. 2.

be supplied either by the arterial transfusion method of Cookson (1954) or by the reverse venous-arterial pump method of Ross (1954a). Unfortunately this increases the surgeon's difficulties by obscuring the field with coronary venous blood, and through the active movements of the heart itself. A stopped heart, even though ischaemic, is not developing a metabolic debt, and the time which can be allowed for deliberate intracardiac repair may be greatly increased under these conditions.

An example of a clinical record of cooling is given in Fig. 2. Here a procedure was completed which could not have been begun without hypothermia. Unfortunately the child died 30 hours later, after showing initial improvement.

DISCUSSION

At present the most obvious application of hypothermia is in those patients with cardiac defects which have a grave prognosis and which cannot be adequately repaired by any technique which does not permit direct visualization of the interior of the heart (certain cases of septal defect), or where central arrest of the circulation must be maintained for a period which would be lethal at normal body temperature (transposition of great vessels, certain cases of pulmonary stenosis and of aortic aneurysm or coarctation). The method is indicated to a lesser degree in any surgical procedure involving a need for temporary but dangerous ischaemia to a part. Reports of its value in experimental asphyxia neonatorum have appeared (Miller and Miller, 1954). The incubator may not be the universal boon it has been thought to be in the management of the newborn (Joppich and Schäfer, 1955). Hypothermia may be used in combination with hypotensive techniques, excluding those in which hypotensive drugs are used because of the tendency for drug accumulation. That an adjuvant method to high spinal hypotension would be useful is suggested by the long list of contra-indications to this technique (Greene, 1952). It is believed by some that hypothermia may eventually have its widest application in the surgery of the poor-risk patient without other special indications; it has certainly not been true for the drug method of reducing autonomic reactivity according to Lassner (1954), who quotes figures showing no improvement in mortality among seriously wounded men.

Many cardiac patients at present cannot be expected to survive surgical interference of any kind, yet 15 to 20 per cent. of cardiac defects cannot be diagnosed by present laboratory and clinical means. Some, particularly in the cyanotic congenital heart group, can be expected to survive operation only if their cyanosis is improved.

This suggests another indication for the use of hypothermia—the exploratory operation in patients in whom pre-operative diagnosis is in doubt, and where error would mean death.

Specific Points of Importance in Regard to Anaesthesia during Hypothermia

1. Cold narcosis potentiates the action of anaesthetics.
2. There is a delay in enzymatic and metabolic breakdown and in excretion of intravenously administered substances.
3. Continuous respiratory exchange must be maintained to prevent hypercapnia and fall in blood pH.
4. Continuous electrocardiographic information is desirable, particularly during induction of anaesthesia and in the early stages of cooling.
5. An electrical defibrillator should be available where cardiac manipulation is contemplated.
6. Direct heat in the form of hot water bottles or electric blankets should not be applied to the patient during rewarming.
7. During hypothermia peripheral arteries are constricted, and it is often difficult or impossible to determine even normal blood pressure levels by the usual auscultatory method. A sensitive electronic device has been developed by D. D. Simpson of the Wilkie Surgical Research Laboratory, Edinburgh, which, without requiring arterial puncture, will accurately indicate blood pressure within a wide range and under these conditions.

Extensive researches into the development of a heart-lung apparatus (Stokes and Gibbon, 1950; Dennis *et al.*, 1951; Melrose, 1953) which will efficiently and safely take over these functions have had only a partial success. Similarly, the use of homologous lungs has not been entirely satisfactory. A voluntary donor for substituting the heart-lung function of a second individual has been successfully used in America, but this is unlikely to become a practicable routine. The ingenious atrial well technique (Gross *et al.*, 1953) has the basic disadvantage of giving accessibility without visibility. The main disadvantages of pump oxygenating systems are these:

1. They are complicated and expensive.
2. They add to the duration and magnitude of the operative procedure.
3. They maintain high pressure coronary flow, with the result that the field in which the surgeon is working requires continual removal of blood by suction.
4. Finally, there is an inexplicable delayed mortality.

On the other hand, cooling itself cannot be carried out without careful preparation. If a man

is exposed to severe cold without anaesthesia, he usually dies before body temperature has reached 27° C. By giving adequate anaesthesia, or by minimizing stimulation of thermal sensitive nerve-endings in skin, body temperatures of 25° C. may be reached with very little risk. Deep anaesthesia, however, reduces the hazard from over-reaction only to impose the danger of under-reactivity, which increases as body temperature falls, making restoration to the normal physiological state more difficult.

The drug method aims at avoiding stress responses by the so-called neuroplegic action of drugs of the phenothiazine group, but falls into the same dangers in resuscitation as does deep anaesthesia and hypothermia.

The cooled, non-stressed, lightly anaesthetized patient is in a safer state than the cooled, stressed, deeply anaesthetized patient. A distinction must be drawn between the behaviour of the cell or organ in ambient cold and the behaviour of the intact organism exposed to external cold. The effect of cold on the former is sedative and protective. The effect on the latter is more complex, involving defence mechanisms and depletion of reserves. This embodies the principle now gaining favour that the body's own attempts to adjust to trauma may be more damaging than trauma itself, and that it is safer for the body to acquiesce to major stresses of injury rather than to allow natural responses to dissipate in vain attrition the body's limited resources. Lowering the metabolic level is one method of achieving this state, but only if the process of cooling in itself does not exact a high expenditure of energy.

Summary

At the present state of development, hypothermia is essentially a protective rather than a therapeutic procedure. Clinical experience is too brief to permit conclusive statements as to its eventual place in medicine, but by its use surgeons have looked upon that last forbidden ground of the body, the interior of the heart, and it is the opinion of many working in this field that hypothermic techniques are more hopeful in this respect than the artificial heart-lung devices so far developed. A combination of pump oxygenating systems and cooling has been suggested (Churchill-Davidson *et al.*, 1953), but unless this gives a clear increase in protection afforded, the combined technical difficulties may make it impracticable. Apart from cardiac surgery, hypothermia protects susceptible organs, such as the brain, liver and kidney against anoxic injury, which might otherwise occur during the hypotensive episodes of major surgery, whether these be deliberate or

spontaneous. This is particularly true for the liver when pre-existing damage is present, as in fourth degree mitral stenosis or portal hypertension. The capillary atony, which is an important factor in the development of irreversible shock, appears to be delayed in hypothermia, and this can be shown experimentally in the prompt recovery of hypothermic animals after periods of low blood pressure which would inevitably be lethal at normal body temperatures.

On the more speculative side, hypothermia might reasonably be considered where surgery must be undertaken during continued haemorrhage or in severe anaemias which cannot be fully corrected. It may be useful in acute infections or in any serious hyperpyrexia. The anaesthetist may bring hypothermia to the aid of the physician in cases of thyrotoxicosis which are refractory to medical treatment. Similarly, coronary thrombosis with cardiac failure may respond to a smoothly lowered metabolic rate. In coronary occlusion the work of the heart would be decreased, tissue oxygen requirements would be less, the viability of infarcted muscle would be protected and further clotting combated by cold. A critical period might be survived and collateral coronary circulation given time to open.

But speculation is swift and must pause for slow experiment.

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in the giving of antitoxin and in the use of drugs which had a depressant effect on the central nervous system. No other means of controlling spasms or convulsions was known. Since the central nervous system is already under attack by the toxin, it would be unwise to add to its difficulties, by adding depressants to the toxin, if there were any other way of reducing muscle spasm. Now that there is another way, the use of depressants in tetanus is dying out, albeit slowly. Some workers (Shackleton, 1954), nevertheless, advocate that light general anaesthesia with nitrous oxide and oxygen should be maintained throughout the period when relaxants are needed, and have had successful results. They argue that light nitrous oxide does not act as a depressant to the vital medullary centres in the same way as morphine, for instance; and that the maintenance of light general anaesthesia reduces, to a fixed level, the otherwise varying amount of sensory and psychic stimulation which makes control so difficult.

The maintenance of general anaesthesia, however—even if it does render control less critical—adds another burden to the already very exacting task of correctly managing a case of severe tetanus with spasticity, convulsions, vagal incoordination, respiratory insufficiency and toxæmia.

Patients who recover from tetanus and from purely bulbar poliomyelitis usually recover abso-

lutely, so that though the treatment of these conditions is exacting and fraught with difficulty, it can be very rewarding.

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