

PROFOUND HYPOTHERMIA WITH EXTRACORPOREAL

CIRCULATION AND THE BUBBLE OXYGENATOR.

A Study with Special References to its Application in Cardiac
Surgery.

....oooOooo....

THESIS

FOR THE DEGREE OF MASTER OF SURGERY.

Presented by

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June, 1961.

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TO MY WIFE.

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CHAPTER ONE.

CHAPTER ONE.INTRODUCTION.

Direct surgical intervention in acquired and congenital defects of the heart is now a reality, largely as a result of a number of techniques which have been evolved following on patient and diligent research.

Surgery on the heart under direct vision usually necessitates the opening of one of its chambers. To achieve this end there must be no circulation through the heart. This is possible in one of two ways: either the whole body circulation is stopped or some system of bypassing the heart is utilised. Total cessation of circulation at normal body temperature for periods of less than 4 minutes is the longest the body can tolerate with safety. Hence moderate surface cooling, and later blood stream (i.e. veno-venous) cooling, was introduced whereby at 29 to 30 degrees centigrade - owing to reduced body metabolism - the circulation to the heart could be interrupted for from 8 to 10 minutes without damaging oxygen-sensitive organs such as the brain and kidneys. This allowed sufficient time in the heart for the repair of the simpler cardiac defects.

The second technique was that of bypassing the heart itself. A pump to do the work of the heart, and in some cases the heart of another person (crossed circulation), was used to replace the patient's heart and maintain his circulation. Most of the variations on this technique incorporated some form of artificial oxygenator, thus allowing both heart and lungs to be bypassed;

but in

but in some, homologous or autogenous lung oxygenation was utilised. When perfected, a number of these techniques allowed a longer time in the heart than hypothermia alone, and more complex defects were tackled. Nevertheless, not one of these techniques is anywhere near perfect and the search continues.

In Cape Town, the DeWall-Lillehei Helix Reservoir Bubble Oxygenator had been used exclusively, first experimentally and then in a large series of clinical cases, with great success. All the operations were performed at normal body temperatures, using high flow rates, and as post-operative morbidity was minimal this technique seemed to be the answer for cardiac surgery.

Nevertheless, the more complex defects, especially those where the high flow rates used caused a large coronary and bronchial return to the heart, still remained very difficult, as did surgery of the aortic valve, with the necessary coronary artery perfusion.

Thus the present study was commenced at the beginning of 1960 to investigate the combination of extracorporeal bypass with blood stream hypothermia. Some workers claimed that this combination offered advantages over either bypass or hypothermia alone. The few reports available at that time on the deeper levels of hypothermia seemed to indicate that this would possibly be the technique of choice of the future. Profound hypothermia may be defined as the deliberate reduction of body temperature by artificial means to below 25 degrees centigrade.

After a

After a review of the literature and some months of study, only two ways of producing profound hypothermia seemed really practicable. Both required an efficient heat exchange unit, which had been obtained and tested in the laboratory by this stage. The one method was the use of bilateral extracorporeal bypass with autogenous oxygenation, and the other was the use of extracorporeal bypass incorporating an artificial oxygenator. A study of both seemed to indicate that the latter method was probably the better one. The artificial oxygenator chosen was the bubble type, as this was the one which was preferred for normothermic perfusion in Cape Town.

This thesis attempts to show that profound hypothermia, with extracorporeal circulation and the bubble oxygenator, is a safe and useful aid in cardiac surgery. In the first part an attempt will be made to correlate the experimental studies, discuss the method which was evolved and point out its safety and usefulness, as well as to discuss the investigations carried out in a search for inherent dangers. In the second part the initial clinical application of the technique will be dealt with, once again discussing the method used, its safety and usefulness.

A statement on profound hypothermia made in a recent publication, bears quotation at this point:

"This particular aspect of hypothermia provides an example of the value of basic research, not immediately applicable to medicine. Out of the early work on isolated tissues, and then small mammals, arises the possibility of deep hypothermia in man which may bring startling new advances in the treatment of heart diseases." (Cooper, 1960).

CHAPTER TWO.

CHAPTER TWO.REVIEW OF THE LITERATURE: THE EVOLUTION OF PROFOUND
HYPOTHERMIA WITH EXTRACORPOREAL CIRCULATION.SECTION A - HISTORICAL REMARKS.

No report on the status of hypothermia in 1960 would be complete without making mention of early workers whose pioneer enthusiasm and observations were to lay the foundation for present day studies.

Hippocrates, in the 5th Century B.C., was probably the first to be aware of the important part played by temperature in human welfare, and he dealt with this in his book "Airs, Waters and Places" (Hippocrates, 5th Century B.C. a). He also advocated snow and ice to check haemorrhage, and was the first to be aware of the analgesic nature of cold (Hippocrates, 5th Century B.C. b). Aristotle, too, realised the importance of body temperature and observed the response of animals to changes in the temperature of their environment (Aristotle, 4th Century B.C.).

Despite these early observations, it was to be many centuries before cold was studied in any detail, and in fact, it was only in the last decade that hypothermia in its various forms became a major field of investigation. During the intervening years, reports on hypothermia appeared sporadically in the literature, but none were followed up in any detail.

Boyle, in investigating the effects of severe cold on animals, was able to show that small animals survived in frozen water for short periods and recovered afterwards (Boyle, 1683). Buffon noted that exposure of animals to cold alone did not produce the

state of

state of hibernation, but instead induced in them a physiologically different "torpid" condition (Buffon, 1749).

During laboratory studies on the effect of intense cold on insects and other animals, Spallanzani was one of the first to use mixtures of ice and various salts to enable him to produce low temperatures (Spallanzani, 1787). At this time, too, the illustrious John Hunter attempted to freeze carp into a state of suspended animation (Hunter, 1766). The concept of total body hypothermia had thus been born.

James Currie investigated the physiological effects of deliberate immersion in cold water, in an effort to determine the cause of death from exposure following shipwreck (Currie, 1789, a). He was probably the first person to notice the "After drop" in temperature which occurred when cooling was stopped (Currie, 1789, b). Later this worker, who was the first to report the experimental reduction of human body temperature, successfully lowered the temperature of a pyrexial patient to 83 degrees Fahrenheit (Currie, 1798).

The use of cold in the form of refrigeration anaesthesia by Baron Larrey, Napoleon's Surgeon-General, was probably the most celebrated instance of this use of hypothermia since the time of Hippocrates. During the campaigns of Russia, Germany and France, he noted that there was no pain during amputations performed on soldiers who had lain on the battlefields at low environmental temperatures (Larrey, 1832). Subsequently, Walther pointed out "that cold produces a state of anaesthesia in which animals are rendered suitable for operative procedures" (Walther, 1862, a). At this early date, this same worker cooled rabbits to 18 - 20 degrees centigrade, rectal temperatures, and observed greatly impaired function of both heart and lungs (Walther, 1862, b).

The great

The great Claude Bernard had, in 1854, already cooled guinea pigs to body temperatures of between 18 and 20 degrees centigrade, using ice, snow, or cold mercury. Later he also investigated other methods of reducing body temperatures (Bernard, 1876, a). In this same work he also observed that temperature determinations made in various vessels within the body cavity showed a definite variation from site to site (Bernard, 1876, b).

Horvath demonstrated that hibernating animals survived cooling to body temperatures of near freezing point, whereas non-hibernators died if the body temperature fell below approximately 19 degrees centigrade (Horvath, 1881). Many workers were intrigued by the phenomenon of hibernation, where certain warm-blooded animals are able to reduce their body temperatures during winter and withdraw into a state of sleep (see Suomalainen, 1956). In this condition, all vital physiological processes are at a minimum and the animals can thus survive the privations of winter. This was one of the lines along which experimental hypothermia progressed, and the experimental work which followed, particularly in the continental schools, showed that artificial hibernation could be induced in non-hibernating animals by body cooling, with little ill-effect, if the natural reactions of the body to cold are prevented by drugs (see Huguenard, 1956).

Meanwhile, work along other lines was also progressing. Langendorff was one of the earliest investigators in the field of perfusion hypothermia. He perfused isolated cats' hearts from an elevated reservoir and studied the temperature effects (Langendorff, 1897). Recent workers have been able to confirm much of Langendorff's work in the intact animal.

The concept

The concept of extracorporeal cooling of animals is certainly not new. In Belgium, Heymans constructed a heat exchanging system, consisting of a glass cannula with a water jacket, at the beginning of World War I. Using this, he cooled and warmed the blood (by means of a carotido-jugular shunt) in more than 300 rabbits (Heymans, 1921). In the words of Gollan:

"These experiments were conducted under the extreme conditions of war and occupation, and Heymans' dedication to Science and Freedom should be honoured by linking his name inseparably to blood cooling".
(Gollan, 1959).

Norman Clark was another worker who studied the effect of cold upon the body. He felt that this brought about a state of suspended animation, which would allow tissues to be preserved intact for considerable periods, while maintaining their potential viability (Clark, 1917).

It had been shown that degenerative changes in tissues could be produced to a marked degree by local refrigeration at temperatures of between 50 and 40 degrees Fahrenheit (Smith and Fay, 1939). Arguing from this work, these authors felt that it was justifiable to employ total body hypothermia in human cancer patients to attempt to reduce the rate of tumour growth and spread. Thus Temple Fay, in November 1938, cooled a patient with disseminated breast carcinoma to 90 degrees Fahrenheit, by means of ice-induced surface hypothermia. This was followed by observations over 100 patients (Fay, 1940; Smith, 1940, a; Smith and Fay, 1940, b). Subsequently, this technique was also applied to psychotic patients by another group of workers (Talbot, 1941). The Nazis, in their horrible experiments at Dachau, made observations as well, on the response of humans to cold when they immersed persons in water at temperatures of between 2 and 12 degrees centigrade (Alexander, 1946).

The probable precursor to present day investigations in hypothermia was the work of Smith and Fay. It was, however, the pioneer work of Bigelow in 1950 which really aroused interest in the possibility of using hypothermia in cardiac surgery, and this has become a clinical reality in the last decade (Bigelow et al, 1950, a, b and c).

SECTION B - THE LAST DECADE.

In the last decade, cardiac surgery has passed through three eras, and today each of these techniques still holds its place. The first was the use of moderate hypothermia alone, the second, the use of the mechanical heart-lung machine alone, and the third, the combination of these two techniques.

It was with a background of sporadic investigation that Bigelow, truly the father of the use of hypothermia for cardiac surgery, commenced his extensive studies in this field. His investigations stimulated the interest of surgeons and research workers all over the world by demonstrating to them the feasibility of using reduced body temperature as an aid in surgery on the heart, and it forms the basis of a host of experimental work. Juvenelle, another pioneer, paid fitting tribute to Bigelow when, in an article on hypothermia, he said:

"We would like to begin this paper by acknowledging how revealing Bigelow's work has been for us, and make it known that his example has been the initiation of our personal contribution in the field." (Juvenelle et al, 1954).

Bigelow's most important contributions were made during 1950. He demonstrated that dogs rendered hypothermic by surface cooling to 20 degrees centigrade were able to survive a 15 minute period

with their ...

with their hearts excluded. Cardiectomy during this phase, however, proved highly lethal. During these experiments, he also practised electrical defibrillation of the heart (Bigelow, Callaghan and Hopps, 1950, a). This work was subsequently carried a step further by observing the alterations which occurred in various parameters in an attempt to define the factors which govern the survival of dogs at low temperatures. Among other factors, he studied the heart rate, the blood and venous pressures, the electrocardiogram and the effect of venesection. He observed that vasoconstriction, vascular stasis and erythrocyte agglutination occurred, and demonstrated that ventricular fibrillation usually caused death between 16 and 22 degrees centigrade (Bigelow, Lindsay and Greenwood, 1950, b). Probably his most significant contribution was the paper entitled "Oxygen Transport and Utilisation in Dogs at Low Body Temperatures", in which he demonstrated that oxygen consumption fell consistently with reduction of body temperature to 18 degrees centigrade, and rose in proportion during re-warming, in a way that was parallel. Bigelow also presented evidence to show that a tissue oxygen deficit did not occur (Bigelow, Lindsay, Harrison, Gordon and Greenwood, 1950, c).

The foundation thus had been laid and the way was open for workers to develop and perfect the technique, prior to its use during cardiac surgery on patients.

Other pioneers of cardiac surgery had by now also recognised the potential value of hypothermia in reducing body metabolism as an aid in their field of surgery. Boerema, a pioneer of blood stream cooling, published his contribution in 1951,

(Boerema,

(Boerema, Wildschut, Schmidt and Breekhuyzen, 1951). Delorme, who introduced arterio-venous cooling in Britain, obtained survivors in dogs cooled to between 22 and 26 degrees centigrade and subjected to an ischaemic insult (Delorme, 1952). Investigators such as Ross (Ross, 1954, a) and Glen (Glen, 1954), continued this work. At the same time, work was being done on a combination of extracorporeal circulation and hypothermia by Gollan (Gollan et al, 1952), Juvenelle (Juvenelle et al, 1954), Peiroe (Peiroe and Polley, 1953) and Senning (Senning, 1954).

Despite this early work on the combination of hypothermia with a cardiopulmonary bypass, it was surface cooling that became the first form of hypothermia to be used and to establish itself. In September, 1952, it became a clinical reality when the first successful operation on the heart under direct vision, utilising hypothermia and venous inflow stasis, was performed (Lewis and Taufie, 1953). The era of surface induced moderate hypothermia as an aid in cardiac surgery had thus commenced.

Various methods of inducing this moderate hypothermia in animals and in patients were evolved over the next few years. Surface cooling was the most widely used. It was usually induced either by packing the patient in ice, or by utilising a cooling blanket through which a refrigerant solution was passed. The immersion of the patient in a cold bath was also extensively practised, and in some clinics the temperature of the operating theatre was reduced, with the patient lying exposed. Unfortunately, the induction of hypothermia by these methods proved to be slow and cumbersome.

Another method, although less commonly used, was blood stream cooling. Following on the investigations of Boerema and Delorme,

Ross studied arterio-venous cooling (Ross, 1954, a). While working in this field, he developed the veno-venous method of inducing moderate hypothermia (Ross, 1954, e). This proved to be satisfactory and was more rapid than surface cooling. By 1956, when it had had a fair clinical trial, Sir Russell Brock was full of praise for the advantages of this method (Brock, 1956).

Body cavity cooling was used by some workers, although it was much less satisfactory than the methods already described. Khalil (Khalil and MacKeith, 1954; Khalil, 1958) and Barnard (Barnard, 1956) introduced the method of gastric cooling, and Ross the method of rectal cooling (Ross, 1955). Other methods of cavity cooling have been discarded. Continental workers also investigated drug-induced artificial hibernation (Haguenard, 1956).

The other method of inducing hypothermia, namely by the incorporation of a heat exchanger in the circuit of a cardio-pulmonary bypass, will be discussed later.

During the early part of the era of surface induced moderate hypothermia, a vast amount of experience in its use was gained, both in cardiac and in other forms of surgery. As a result of its clinical application in centres all over the world, the dangers and limitations of this method soon became very obvious. This led to a wealth of experimental work on the physiological changes occurring during its application, and thus to the evolution of methods to decrease its number of shortcomings.

In 1941, Dill had already made observations on the metabolic variations that occurred in surface-cooled patients, with special reference to the acid-base balance (Dill and Forbes, 1941).

Bigelow, however, was the first to perform any really detailed studies (Bigelow et al, 1950, b and c), and by 1957 he felt that the three major complications were ventricular fibrillation, rewarming shock and an increased bleeding tendency. He made a study of these three aspects (Waddell, Fairley and Bigelow, 1957). Delorme investigated local ischaemia, at times lethal at normal body temperature, and showed that dogs subjected to hypothermia could survive this (Delorme, 1952). Glen confirmed this, and also showed that total exsanguination could be survived at low body temperatures (Glen, 1954). Ross, too, made extensive physiological observations on dogs (Ross, 1954, b).

Ventricular fibrillation, one of the major drawbacks, was investigated extensively. In 1956, Covino felt that a combination of hyperventilation and "ambonestyl" could reduce its incidence during surface cooling to nil (Covino and Hegnauer, 1956), but his hopes for this combination were obviously not borne out by his later work, as he was still investigating the problem in 1959. By then he felt that there were two forms of ventricular fibrillation: a spontaneous form occurring with cooling, which was significantly reduced by "nephentermine", and a surgically induced variety, significantly reduced by quinidine (Covino, Margolis and D'Amato, 1959). To overcome ventricular fibrillation once it had occurred, Senning advocated massage, adrenaline, further massage and finally electroshock (Senning, Abe and Melina, 1956). Many workers realised that surface cooling would be safe if ventricular fibrillation could be prevented (Gollan et al, 1955, a; Fisher et al, 1958; Corssen et al, 1959). Thus the protective effect of hypertonic glucose and sucrose on its incidence was studied (Beavers, 1959, a), and it was shown that intravenous heparin and a 5 percent solution of dextrose in water reduced the terminal temperature due to ventricular

fibrillation ...

fibrillation or arrest (Coranna, Montgomery and Swan, 1959).

The rearming shock, which Bigelow feared, was studied by workers such as Blair (Blair, Montgomery and Swan, 1956), and others.

Another factor that disturbed many people was the possibility of an increased bleeding tendency. Willson demonstrated a prolonged clotting time. He felt this to be due to a diminution of platelets, due to their sticking to the venule walls (Willson, Miller and Elliot, 1958). Von Kaula, however, was able to show that during heart surgery in man, recalcification time and prothrombin consumption time were not impaired (von Kaula and Swan, 1958).

Phyllis Knecker induced hypothermia in dogs. The histological changes which she observed in the liver, the kidney and the adrenal led her to conclude that this form of hypothermia was dangerous and should not be used (Knecker, 1955, a and b). Her work was disturbing to many people, even though subsequent investigations failed to confirm her findings, (Fisher, Feder and Fisher, 1957; Kaufman, Gavan and Hill, 1958; Gollan, 1959).

It was becoming more and more obvious that this form of moderate hypothermia was not the answer to the problem of open intracardiac surgery. In addition, it only allowed a maximum period of 8 to 10 minutes inside the heart, thus the more complex defects still remained beyond the reach of the surgeon.

In the meantime, a number of investigators had been developing a mechanical substitute for the heart and lungs to allow more time for the surgeon to correct anomalies such as ventricular septal defects and tetralogy of Fallot malformations.

This

This eventually led to the development of the heart-lung machine which made it possible to bypass the heart and lungs for some hours (Miller, Gibbon and Gibbon, 1951; DeWall et al, 1956; Gross et al, 1956; Kolff et al, 1956).

These heart-lung machines opened the next era in cardiac surgery, as many more pathological conditions of the heart became amenable to surgery. The various techniques were used and improved in clinics all over the world. Of the available oxygenators, the Cape Town clinic uses the DeWall-Lillehei bubble oxygenator exclusively for all normothermic cardiopulmonary bypasses, both in the experimental animal laboratory (McKenzie and Barnard, 1958), and in their clinical cases (Barnard et al, 1959; Barnard, McKenzie and de Villiers, 1960). Despite the many improvements and refinements that were introduced, these artificial oxygenators, when used in association with high flow rates for normal body temperature perfusions, still presented difficulties, especially in the more complicated cardiac cases.

Thus the search for new and better methods continued. In this search the workers in the two fields that have been discussed so far all progressed. The protagonists of normothermic cardiopulmonary bypass improved their technique to the point where their results were excellent. The exponents of moderate hypothermia were looking for ways of increasing the time available in the heart. Spencer developed a method of coronary perfusion in surface cooled hypothermic cases with secundum atrial septal defects, thus increasing the circulatory occlusion time to the safe time for the brain (Spencer and Bahnon, 1959). Other workers described similar techniques (DeWeese, Jones, McCoord and Mahoney, 1959).

It was

It was Bigelow again, in a review of the status of hypothermia in 1958, who suggested that one of the research projects that held hope for the future solution of the problem was the combination of hypothermia with cardiopulmonary bypass (Bigelow, 1958). It was not long before the truth of this statement was demonstrated. In actual fact many of the pioneers in cardiac surgery before that time had used such a combination, and in this respect Gollan's work holds a place of importance that is second only to Bigelow's in the field of hypothermia (see Gollan, 1959).

As has been pointed out, it was the failure of heart action, or the commencement of ventricular fibrillation, which occur as the body temperature is reduced, that limited the applicability of the conventional forms of hypothermia. Thus, although the oxygen demands of the vital organs are reduced, this reduced requirement was not met. On the other hand, high flow rate cardiac bypass has its limitations. The low flow principle in heart-lung machines had been introduced in 1954 (Warden, Cohen, Read and Lillehei, 1954), as a result of azygous flow studies (Andreason and Watson, 1952), but was unsound in principle as the body did not receive its full oxygen requirements and waste products accumulated.

The obvious answer was the combination of the low flow principle of cardiac bypass with hypothermia. Then, although the circulation was less than normal, it was adequate in the presence of the decreased demands of the body brought about by the cooling. Many people feared that this combination would add the disadvantages and the dangers of the two techniques. It was, however, soon to be shown that, in fact, the combination brought out many of the advantages of both while excluding some of the disadvantages.

In 1952

In 1952, Gollan published his pioneer article in this field. Although others had used extracorporeal cooling before him (see Chapter Two, Section A "Historical Review") his work, together with that of certain other pioneers, was to be the forerunner of present day successful techniques. Using bubble oxygenation with a veno-arterial shunt in closed chest dogs, he was able to cool them to 29 degrees centigrade and obtain survivors (Gollan, Blos and Schuman, 1952). Two years later, using a gas dispersion oxygenator with hypothermia, he was able to obtain 15 survivors consecutively in dogs (Gollan, Hamilton and Meneely, 1954). At about the same time, on the continent, Juvenelle and his co-workers were working along similar lines. In their article, written in 1952 and published in the English literature in 1954, they state that "we convinced ourselves that the gross biochemical changes taking place during refrigeration were reversible, and comparable in many respects to what is seen in the hibernating animal. Since this study showed no real damaging action due to hypothermia, we started the work on extracorporeal circulation combined with hypothermia." In their experiments they first inserted the catheters into the dogs and then cooled them in an ice water bath. When the dogs' circulation began to fail, they commenced the extracorporeal bypass, using either a small oxygenator or homologous dog lungs. As a result of their work, they concluded that: "It is possible in dogs to lower the body temperature to levels ranging from 12 to 16°C, to replace the circulation by a simple perfusion method during ventricular fibrillation exceeding three hours, to control this fibrillation through the unopened chest, and to have the animal return to normal life Further technical developments are highly needed in view of human application" (Juvenelle, Lind and Wegelius, 1954).

Another

Another early investigator in this field was Peirce, who used a low capacity pump oxygenator system, incorporating a heat exchanger, and utilised homologous dog lungs for oxygenation (Peirce and Pelley, 1953).

On the basis of this early work has developed the concept of low flow extracorporeal circulation, associated with moderate hypothermia, produced and controlled by an efficient heat exchanger incorporated in the circuit. It was the work and the numerous publications of Sealy and his group in the United States that really put this technique on a sound footing as a safe and useful aid in cardiac surgery. Thus the third era of cardiac surgery in this decade had commenced.

Prior to its clinical application, further work was performed with dogs. Even before the introduction of their heat exchanger, Sealy's group showed that low flow extracorporeal circulation was safe, and allowed cardiac arrest of up to 21 minutes in dogs at temperatures of about 30 degrees centigrade, with subsequent survival (Sealy, Brown, Young, Stephen, Harris and Merrit, 1957). They later included their heat exchanger in this system (Brown et al, 1958, a and b). By this time Peirce was getting his best survival in dogs by utilising homologous dog lungs for oxygenation. He did not actively rewarm the dogs' blood for fear of liberating oxygen bubbles (Peirce, Babbs, Rogers, Rawson and Tompkins, 1958). This fear of oxygen embolisation, although very real in the minds of these early workers, has not proved to be a problem, and Sealy states that embolism has never occurred in their clinical studies or in their laboratory experiments (Sealy et al, 1959, a; Sealy et al, 1958, b; Lesage et al, 1959; Gollan, 1959; Urschel et al, 1960; Gerbode et al, 1960, a).

After ...

After preliminary work in dogs, investigators soon employed the technique in patients undergoing cardiac operations. As occurred in the case of surface hypothermia, investigations into the physiological variations that took place in people subjected to the technique were continued throughout this period until the present time. Once again, it was Sealy and his group who made the most important contributions in this field. They demonstrated that cardiac arrest produced by their method of using potassium, magnesium and prostigaine, and continued for up to 17 minutes, was safe in people at temperatures in the region of 30 degrees centigrade (Sealy, Brown, Young, Stephen, Harris and Merrit, 1957; Sealy et al, 1958, b). Using their own heat exchanger (Brown, Smith and Emmons, 1958, a), they investigated various parameters, including the temperature gradients that occurred (Brown, Smith, Young and Sealy, 1958, b). They demonstrated that only minor variations in lactic acid levels in the blood occurred as a result of this procedure and they were able to show clearly the safety of this combination when used in conjunction with a DeWall-Lillehei bubble oxygenator (Sealy, Brown and Young, 1958, a). Elsewhere they discussed their investigations into acid base balance and oxygen consumption, and in the light of their findings they felt it to be a safe technique for use in patients (Young, Sealy, Brown, Smith, Callaway and Harris, 1959). E.E.G. monitoring was also found to be a useful aid (Stephen, Bourgeois-Gavardin, Dent, Brown and Sealy, 1959).

Other workers in this field include Gerbode, who has had better survival and morbidity since he commenced using the combined technique (Gerbode, Osborn and Johnston, 1960, a; Osborn, Bramson and Gerbode, 1960; Gerbode et al, 1960, b).

Nixon incorporated a bubble trap when he used this technique (Nixon, Grimshaw, Catchpole, Snow and Lawrence, 1960).

Probably one of the most important requirements when using this technique is an efficient heat exchanger which does not cause excessive blood destruction. Many workers have developed their own, and most of these meet the requirements. The one developed by Brown is probably the most widely used today (Brown et al, 1958, a and b); Heinbecker's one is merely a modification of this (Heinbecker et al, 1959); Gollan developed his own (Gollan, 1959) as did Peirce (Peirce et al, 1958). Urschel's heat exchanger is an integral part of their Kay-Cross oxygenator (Urschel et al, 1960) and Zuhdi's forms an integral part of the bubble oxygenator (Zuhdi et al, 1960, a and b). Gerbode's one is incorporated in their larger rotating disc oxygenator (Gerbode et al, 1960, a and b). Musicant uses a Kay-Anderson oxygenator, which is made of stainless steel. He does not warm it as is usual, and this gives hypothermia of about 31 degrees centigrade in 2 minutes. His patients are allowed to rewarm on their own (Musicant et al, 1959). In Cape Town the Bannington heat exchanger has been used (Terblanche and Barnard, 1960; Barnard, Terblanche and Ozinsky, 1961).

As more and more cases were done using this combined technique, its many advantages became apparent. Some of the advantages noted were: the oxygenators did not have to produce very high flow rates; the reduced bronchial and coronary return afforded the surgeon a clearer view inside the heart; the cold cardioplegia produced was safer than chemical cardioplegia (Gott et al, 1959; Gerbode et al, 1960, a).

Urschel

Urschel also demonstrated the safety of cold cardioplegia (Urschel et al, 1959). Another advantage was the simplicity of the set-up. The danger of ventricular fibrillation, the increased bleeding tendency, the limited time available for the surgeon to work inside the heart, and the rewarming shock of external hypothermia were obviated (Zuhdi et al, 1960, a). Sealy also pointed out that cardiac irritation was no longer a problem (Sealy et al, 1958). Blood cooling was considerably more efficient than in immersion cooling. The vital organs were cooled quickly and the temperature was easily controlled, especially in an emergency (Peirce et al, 1958; Sealy et al, 1958). In addition, the hypothermic heart tolerates ischaemia much better than at normal temperatures (Sealy et al, 1958), and the postoperative metabolic acidosis was not marked (Young et al, 1959).

It can thus be seen that moderate hypothermia, in association with extracorporeal circulation and cardiopulmonary bypass, had firmly established itself as one of the most useful aids to intracardiac surgery by the beginning of 1960. The way was now open for the development of the final stage, namely the extracorporeal circulation associated with deeper levels of hypothermia.

SECTION G - PROFOUND HYPOTHERMIA.

So far, the pioneer work done in hypothermia by the early investigators has been mentioned, as well as the numerous aspects of moderate hypothermia in relation to cardiac surgery that have been studied in the last decade.

In

In another field, as a result of the early work on isolated tissues and then on small animals, arose the possibility of the use of the deeper levels of hypothermia in larger mammals, and then in man (see Cooper, 1960). A considerable amount of important work on profound hypothermia in smaller animals has been performed by people such as Adolph, Andjus, Niasi and Smith (Adolph, 1948; Adolph, 1951; Andjus and Smith, 1954; Andjus, 1955 a; Andjus and Lovelock, 1955 b; Andjus and Smith, 1955 c; Niasi and Lewis, 1954; Smith, 1954 a; Smith, Lovelock and Parkes, 1954 b). Then, when they had overcome the danger of ventricular fibrillation by various manoeuvres (Gollan et al, 1955 a; Niasi and Lewis, 1956; Covino et al, 1959), certain workers obtained survivors in larger mammals after surface cooling to temperatures below moderate levels.

This, on the one hand, had developed the technique of moderate hypothermia in association with extracorporeal circulation, and, on the other hand, profound levels of hypothermia were also being used, first in small and later in larger mammals. Once again it was the pioneers, Gollan and Juvenelle, who used these two techniques in combination in the early days of experimental cardiac surgery. Over the last two years, on the basis of their work, later investigators were able to develop this combination of profound levels of hypothermia with cardiac bypass to the present fairly advanced stage.

In his early work Gollan noted that when he cooled dogs with closed chests on cardiopulmonary bypass to below 29 degrees centigrade, they died of ventricular fibrillation (Gollan, Elos, and Schuman, 1952). Juvenelle, however, managed to overcome this difficulty even in dogs with unopened chests, which he cooled to between 12 and 16 degrees centigrade (Juvenelle, Lind and Wegelius, 1954). Later, when Gollan opened the dogs' chests,

he also obtained survivors (Gollan, Hamilton and Meneely, 1954). He followed this with a host of experimental work in the same field and obtained a fairly good survival rate in dogs in which he had produced differential hypothermia of as low as 0 degrees centigrade (Gollan et al, 1955 a, b and c). At this stage he was having trouble with delayed shock in his dogs, and instituted vigorous cortisone therapy to prevent this (Gollan, Phillips, Grace and Jones, 1955, a). Although it had been suggested that profound cooling was not feasible, because the oxygen dissociation diminished with cooling, he noted that another factor more than compensated for this disturbance. As the temperature was reduced, so the direct solubility of oxygen in physical solution in the blood increased (Gollan, Tysinger, Grace, Kory and Meneely, 1955, b). In 1957, Kenyon's preliminary report appeared from Britain. This article described the cooling of dogs to below 10 degrees centigrade with cardiac recovery on rewarming (Kenyon and Ludbrook, 1957).

Before the advent of 1959, Gollan was convinced that the hope for the future of cardiac surgery lay in this technique. He stated: "It is my conviction that hypothermia of 0°C is compatible with life of adult, large, non-hibernating mammals, if adequate perfusion of the vital organs is maintained." (Gollan, 1959). During 1959, further experimental work was performed, and this year marked the beginning of the fourth - and present - era of cardiac surgery, as patients were subjected to profound hypothermia for the first time.

On the experimental side, Sealy's group investigated thoroughly the possibility of profound hypothermia produced by their heat exchanger associated with low flow cardiopulmonary bypass (Sealy, Lesage and Young, 1959, b; Lesage, Sealy, Brown and Young, 1959). Heimbecker cooled dogs to 10 degrees

centigrade /.....

centigrade (Heinbecker, Young and Sanford, 1959), and Kenyon reported on a large series of dogs (Kenyon, Ludbrook, Downs, Tait, Brooks and Fryszkowski, 1959). These workers all incorporated an artificial oxygenator in their bypass circuit. The applicability of their technique to cardiac surgery was becoming more and more obvious.

Quite early, Sealy's group cooled a case with a severe tetralogy of Fallot malformation down to 9.3 degrees centigrade and stopped the perfusion completely for a few minutes on three different occasions (Young, Sealy, Brown, Smith, Callaway and Harris, 1959). Elsewhere they reported on 7 cardiac patients cooled to between 9 and 20 degrees centigrade. As a result of their observations, they stated that temperatures of between 15 and 20 degrees centigrade offer almost as much reduction of oxygen needs as temperatures below 10 degrees centigrade. They also demonstrated that profound hypothermia not only protects the heart from ischaemia, but may in addition be used to produce cardiac standstill (Sealy, Brown, Young, Smith and Lesage, 1959, a).

In the meanwhile, workers were investigating a different combination of profound hypothermia with extracorporeal circulation. In the past, because of the dangers and difficulties present in the oxygenation of venous blood outside the body, the possibility of autogenous oxygenation (the use of the patient's own lungs for oxygenation), which dispenses with the artificial oxygenator, was studied (Wesolowski and Welch, 1952; Cohen and Lillehei, 1953; Read, George, Cohen and Lillehei, 1956; Cooley, DeBakey and Morris, 1957; Mustard, Sapirostein and Fav, 1958). These studies were carried out at normal body temperatures, and were not received with much enthusiasm. It was only when Shields

and /.....

and Lewis, and Drew's group, working independently, combined it with profound hypothermia, that interest was renewed (Shields and Lewis, 1959; Drew, Keen and Benason, 1959, a). In this technique each side of the heart is individually bypassed, using two separate extracorporeal circulations. The animals' lungs were thus maintained in the circuit to enable them to perform their normal function of oxygenating the blood. The heat exchanger is incorporated in one or both of the circuits. According to Shields, it appeared to hold a number of distinct advantages and was close to their ideal of obtaining a short period of cooling, a long bloodless period, rapid rewarming, an uncomplicated mechanical system, a low priming blood volume and no oxygenator (Shields and Lewis, 1959).

Despite the fact that the survival rate in Drew's experiments was poor, they extended the use of this technique to their cardiac patients with success. They report on 7 patients who were cooled to about 15 degrees centigrade. The circulation was stopped completely for up to 45 minutes with safety, while the intracardiac repair was performed. Any catheters in the way were removed during this period. The patients were then rewarmed on cardiac bypass. In this group only two deaths occurred, both due to postoperative heart block (Drew and Anderson, 1959, b).

Thus, at the end of 1959 and beginning of 1960, when the present study was commenced, there were two feasible methods of producing profound hypothermia. Both had been used on only a very limited number of patients, but with apparent success. The promise of an unhurried repair of cardiac defects, in what almost amounted to post-mortem conditions, led many workers to investigate the possibilities of profound hypothermia. As the months of 1960 passed, more and more reports appeared in the literature of its successful use, both in dogs and in patients.

Archer Gordon, in the United States, who had studied both methods, felt that the "Drew technique" was the better (Gordon, 1960, b). Using autogenous oxygenation, he induced profound hypothermia in 30 dogs with a good survival rate. In 10 dogs he studied the oxygen consumption and, on the basis of this study, devised a table in which he set out the arbitrary safe lengths of time for circulatory occlusion at various temperatures. Following on his experimental work, he commenced using the technique in patients undergoing cardiac surgery and reported on the first 21 cases, in which he had a 23.8 percent mortality. He found that no major disturbance in the acid base balance occurred and, in fact, he administered no sodium bicarbonate after his perfusions (Gordon, Jones, Luddington and Meyer, 1960, a). Benason, in a paper discussing the anaesthetic aspects of Drew's work, pointed out that an independent psychiatric assessment of the cases subjected to profound hypothermia with autogenous oxygenation and complete circulatory arrest, had shown no evidence of cerebral disturbance post-operatively (Benason, 1960). This is another indication of the safety of profound hypothermia. Holt also studied profound hypothermia induced in dogs by this method (Holt, Macalalad and Lewis, 1960).

Despite the enthusiasm of these groups for the autogenous oxygenation technique of profound hypothermia, other workers who had tried both methods preferred to use an artificial oxygenator in the system. In the former technique, multiple cannulation of the heart was necessary. In order to facilitate the operative procedures, the circulation had to be completely stopped, usually so that the catheters which were in the way could be removed. Today, most people would agree that a low flow rate maintained during surgery is preferable to no flow at all as, even at the profound levels of hypothermia used, there is still a small demand for oxygen. These low flow rates serve to minimise any possible

metabolic acidosis that might occur from the accumulation of metabolites, as a result of the minimal metabolism taking place.

Thus the writer (Terblanche and Barnard, 1960), like Gerbode, "took a long, hard look at the Drew technique" and eventually decided that the incorporation of the oxygenator "increases the safety, and allows for considerably more versatility during difficult procedures" (Gerbode, 1960, e). Simpson, in his experimental laboratory, started with the "Drew technique" but added a DeWall oxygenator to the circuit prior to using it clinically (Simpson, Gibson and Bloomfield, 1960). Other workers in the field have also expressed a preference for the addition of an artificial oxygenator. Urschel reported on 11 dogs subjected to profound hypothermia, using an oxygenator with an integral heat exchanger (Urschel, Greenberg and Roth, 1960). Johnson subjected 15 dogs with closed chests to 22 coolings. Intravenous quinidine was used to prevent ventricular fibrillation, which occurred in only two instances. In his controls, however, it occurred in every case (Johnson, Lesage, Floyd, Young and Sealy, 1960). His work indicated that non-cardiac procedures in patients under profound hypothermia may be performed in the future, without the presence of an open chest.

Sealy's group, in another paper, reported on a large series of dogs rendered profoundly hypothermic on cardio-pulmonary bypass, both with and without total cessation of circulation, in the lower temperature ranges. They again demonstrated the value of intravenous quinidine in preventing ventricular fibrillation and, like Gordon, they studied oxygen consumption at the various temperatures. They have extended

the use /....

the use of this procedure to 33 cardiac and 3 neurosurgical patients, with a 30 percent mortality. They used the bubble oxygenator in association with their own heat exchanger, and like other workers, were full of praise for the advantages of the technique (Sealy, Young, Brown, Smith and Lesage, 1960). The Cape Town group has also reported on their first 25 cases using the bubble oxygenator in conjunction with profound hypothermia (Barnard, Terblanche and Ozinsky, 1961).

One of the largest published series was that of Gerbode and his associates. They have combined cardiopulmonary bypass with hypothermia in 190 patients, 59 of these being performed under profound hypothermia. They, too, discussed the many advantages of this procedure and demonstrated that only a minimal metabolic upset occurred as a result of its application. They report that one of their cases developed oliguria, but recovered (Gerbode, Osborn and Johnston, 1960, a; Osborn, Bramson and Gerbode, 1960). In another paper, they emphasize the important point that left atrial drainage must be instituted as soon as ventricular fibrillation occurs, to prevent left heart over-distention (Gerbode, Osborn, Bramson, Harkins, Ross and Johnston, 1960, b). Ross has reported 25 cases, but not all of these were cooled to the stage of profound hypothermia (Ross, 1960).

Thus it would seem, in the light of present day knowledge, that profound hypothermia is best produced by a combination of an extracorporeal circuit, an efficient artificial oxygenator and a good heat exchange unit. "Its use promises much in the development of intracardiac surgery, but the technique is as yet in its infancy So far, the number of patients subjected to deep hypothermia is small It may be some years before we can safely steer between the first rush of pioneer enthusiasm
and /.....

and overbiased inhibitory conservation" (Cooper, 1960).

In this chapter, an attempt has been made to trace the development of hypothermia to its present status, where the use of the profound levels is establishing itself as a useful and necessary aid to cardiac and other forms of surgery, and, at the same time, to pay due tribute to the many pioneers and research workers involved. Only through their painstaking work does hypothermia hold its place of importance today.

CHAPTER THREE.

CHAPTER THREE.

EXPERIMENTAL INVESTIGATIONS IN PROFOUND HYPOTHERMIA USING THE BUBBLE OXYGENATOR IN DOGS.

SECTION A - INTRODUCTION.

By the time the present study was commenced at the beginning of 1960, a large number of dogs, and 120 clinical cases, had been reported successfully subjected to normothermic perfusions by workers in the Cape Town clinic, using the DeWall-Lillehei helix reservoir bubble oxygenator (McKenzie and Barnard, 1958; Barnard, McKenzie and de Villiers, 1960). This technique, although extremely useful, still had limitations and disadvantages. The few reports of earlier workers which had appeared in the literature (See Chapter Two) seemed to indicate that, by the addition of profound hypothermia to this technique, an even better aid to intracardiac surgery might be evolved. As a result, the present investigations in the field of cardiac bypass associated with profound hypothermia were commenced.

Most of the methods of profound hypothermic cardiac bypass that have been investigated in this study involved the use of the bubble oxygenator in a similar circuit to that used in normothermic perfusions in Cape Town. Certain modifications have been introduced since the oxygenator was originally used, therefore the circuit as used at present for normothermic perfusions will be discussed first.

Figure III, 1, is a diagrammatic representation of the bubble oxygenator. The fundamental part of this artificial oxygenator is the mixing chamber which, like so many parts of

the /.....

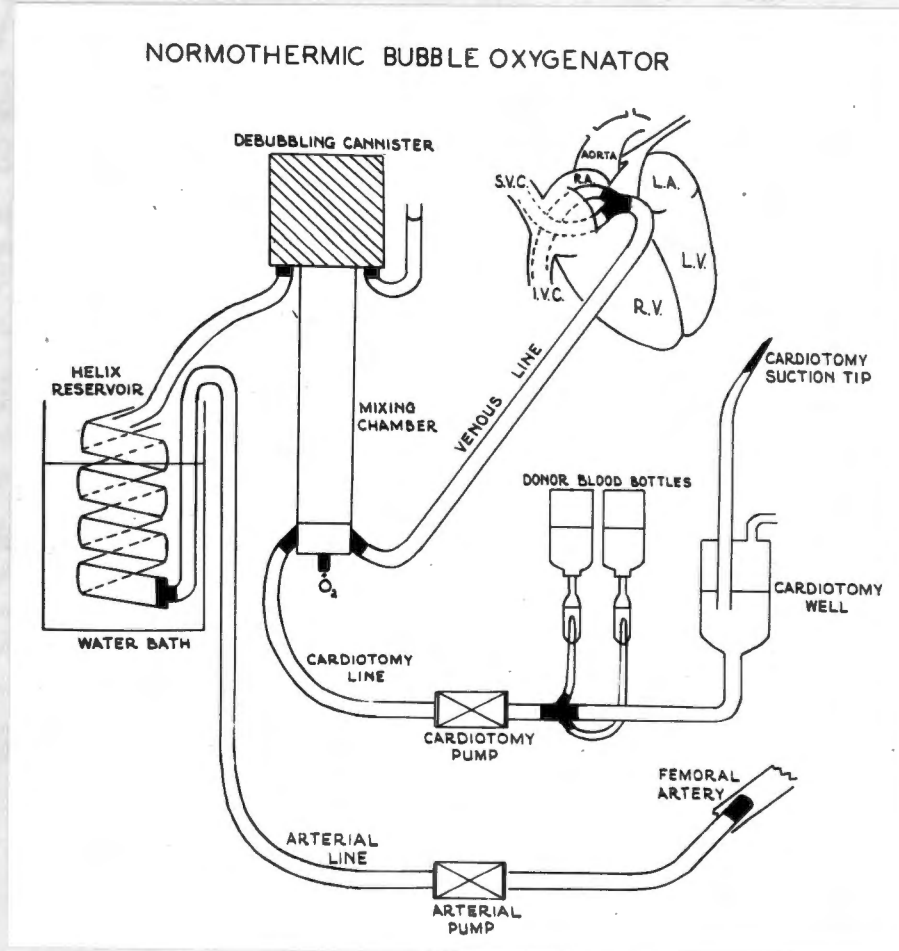


FIGURE III, 1.

A diagrammatic representation of the DeWall/Lillehei Helix Reservoir bubble oxygenator system, as it is used for normothermic perfusions in Cape Town.

the system, is made from pure, polyvinyl plastic hose. Here the exchange of gases takes place, on the surface of oxygen bubbles. At its upper end is the debubbling cannister, where the gas bubbles are broken down as the blood/gas mixture flows over stainless steel sponges. These sponges have been prepared previously by dipping into a debubbling substance, Antifoam A, and baking this onto the sponges. The liberated gas escapes while the oxygenated blood passes through the nylon gravity filter, situated in the cannister, and then into the helix reservoir. This reservoir today performs three functions: firstly, as its name implies, it serves as a reservoir; secondly, by means of marks at 100 cc. levels, the blood balance of the bypass can be estimated; thirdly, by placing it in a warm water bath, the blood is kept at normal body temperature. During the actual cardiopulmonary bypass, the de-oxygenated venous blood drains by gravity from the venae cavae, via the venous line, to enter the bottom of the mixing chamber, where it is filmed on oxygen bubbles. The blood is oxygenated, debubbled and then passes into the helix reservoir. From here it is pumped via one head of a Sigmator pump back into the dog through a femoral artery. The apparatus also has a cardiotomy return system. Blood from the operative field in the heart is sucked into the cardiotomy well by means of a suction pump attached to the top of the well. From here the blood is pumped via the cardiotomy pump (the second head of the Sigmator pump) into the oxygenator system at the base of the mixing chamber. The priming of the apparatus with donor blood is also performed through the cardiotomy pump.

When this study was begun, it seemed reasonable to try to include some form of heat exchange system as an integral part of this oxygenator, which was already being successfully used in the laboratory. This would obviate the necessity for extra

priming /....

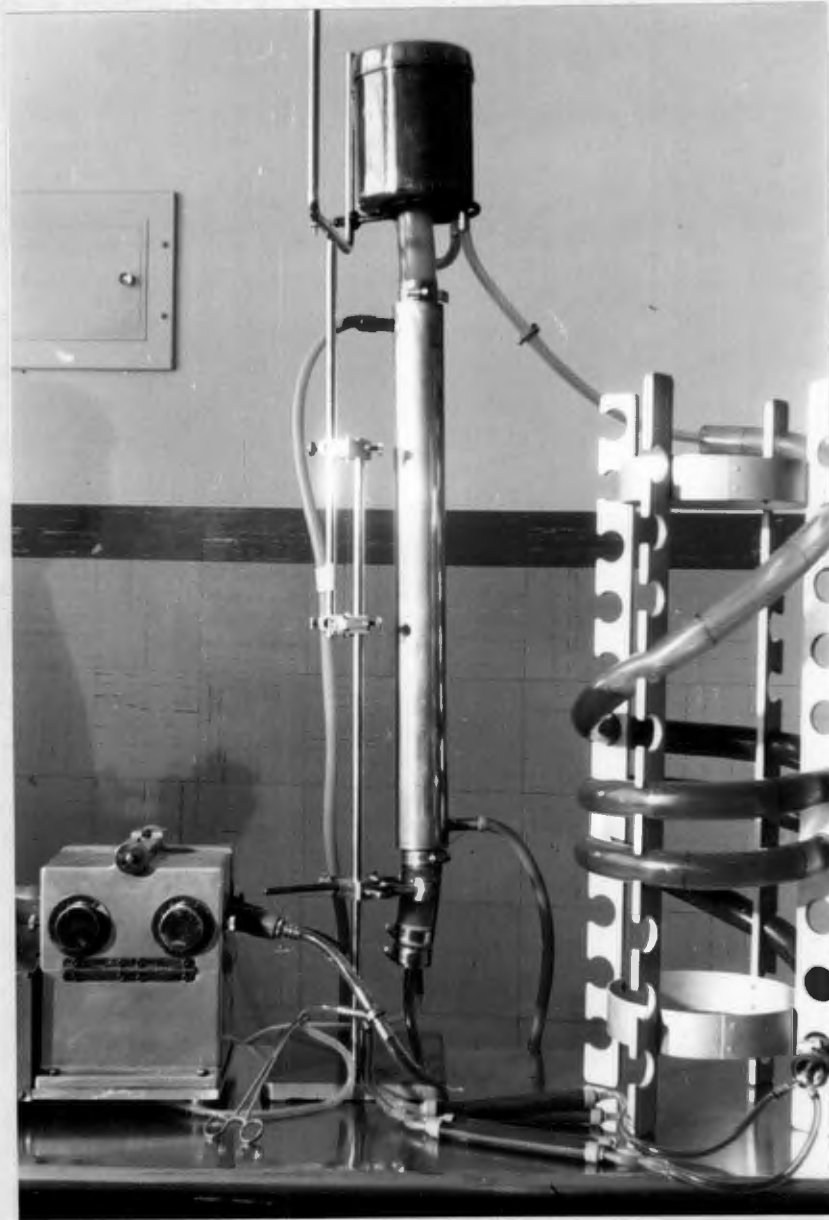


FIGURE III, 2.

**An integral Heat Exchanger incorporated
in the mixing chamber of the bubble
oxygenator.**

priming blood for the heat exchanger itself. The two obvious situations where such an integral heat exchanger could be included were those where the blood moves relatively slowly, namely the mixing chamber and the reservoir.

The first move was to design a heat exchange system to be incorporated in the mixing chamber (Figure III, 2). In principle, it consisted of an outer jacket for the mixing chamber, through which the cooling and warming fluid could be passed. Six experiments were performed using this model. The method, although successful in cooling the animals, was too slow and was discarded at this stage.

The reservoir was then tried. A large heat exchanger designed locally was available in the laboratory. The principle on which it worked was that the blood flowed over the outside of stainless steel tubes, through which the cooling fluid was passed. The whole unit was encased in a transparent Mayon outer jacket and the blood thus remained visible. This heat exchanger had proved impracticable if placed in the arterial line because of its high priming volume, which was about one litre. By incorporating it as part of the reservoir, this problem was overcome and no extra priming blood was required. In Figure III, 3, this heat exchanger is seen forming the lower part of the reservoir, situated next to the mixing chamber. Its efficiency in this situation was tested in seven dogs and, as in the first method tried, both cooling and rewarming proved to be too slow to be of use clinically, although low temperatures were easily attained.

These two methods, although discarded at this stage, gave invaluable experience in profound hypothermia induced in dogs using the bubble oxygenator, and served as a forerunner to the development of the present technique.

At this /....

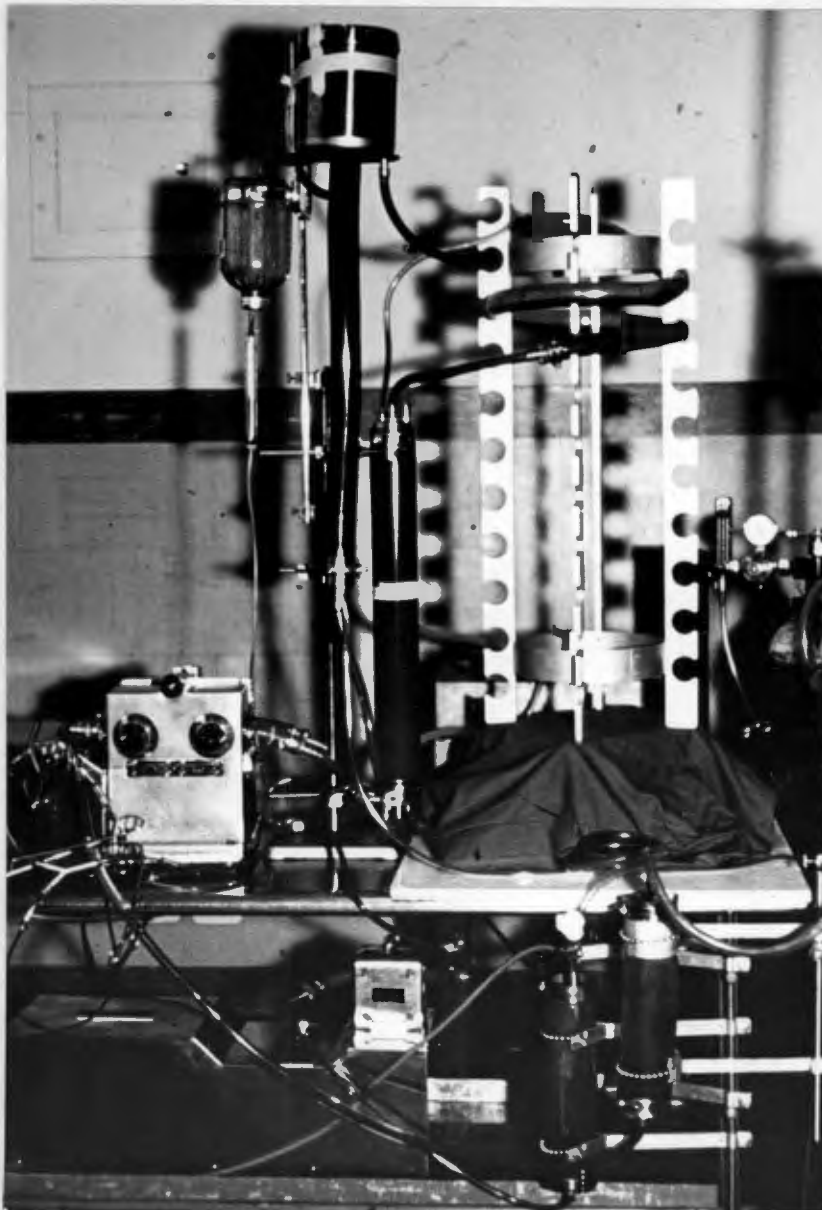


FIGURE III, 3.

An integral Heat Exchanger incorporated in the reservoir of the bubble oxygenator. It is situated between the mixing chamber and the Helix Reservoir stand, forming the lower portion of the reservoir.

At this stage, the Bennington heat exchange unit, which will be described later, was made available for trial in the laboratory. Since it was tested and found suitable and most efficient, it has been used exclusively in all the subsequent experimental work on profound hypothermia.

By this time it appeared that, with the incorporation of an efficient heat exchanger in the bubble oxygenator system, a good method of producing profound hypothermia clinically could be evolved. Nevertheless, the work of Shields, and of Drew, and their co-workers, also indicated that the use of autogenous oxygenation in a bypass circuit with a heat exchange unit might be another suitable method of producing profound hypothermia (Shields and Lewis, 1959; Drew et al, 1959, a and b). This technique was therefore tested in 13 dogs, with a good survival rate, one of the long-term survivors having had his circulation stopped for 60 minutes during the hypothermic phase (Terblanche and Barnard, 1960).

On assessing the two techniques, however, it was clear that the inclusion of an artificial oxygenator in the system would be preferable to the use of autogenous oxygenation in producing profound hypothermia in patients.

With all this experience in inducing profound hypothermia in dogs, the evolution of the present technique was a fairly simple matter. The Bennington heat exchange unit was merely incorporated in the arterial line of the standard bubble oxygenator circuit.

There was no doubt that a multiplicity of unknown variables would be met when a homeotherm's body temperature was reduced to profound levels. Apart from studying the safety of the technical aspect, it seemed necessary to study the parts played at least by some of these variants in the long-term safety of

the /...

DOG NO. & WEIGHT	NATURE OF EXPERIMENT	BYPASS DETAILS IN MINS.	TOTAL DURATION OF BYPASS	PLASMA HB	LOWEST TEMP. IN OESOPH IN °C	SURVIVED 24 HRS. POST BYPASS.
1 15 KG.	PROLONGED CIRC. ARREST	30 C. 18-20 HRS F. 40 W.	70 MINS + 18-20 HRS OFF	—	6.9° C	NO
2 15 KG.	RENAL 1.	30 C. 30 OFF 30 W.	60 MINS + 30 MINS OFF	—	11° C	YES ^x
3 21 KG.	RENAL 2.	NORMO. COOLING COLD WARMING	106 MINS	54 mgms%	9.3° C	YES ^x
4. 17 KG.	RENAL 3.	10 NORMO. 10 25° C 10 10° C WARMING	89 MINS	48 mgms%	11° C	YES ^x
5 20 KG.	RENAL 4.	DO.	71 MINS	112 mgms%	10.2° C	NO
6 17 KG.	RENAL 5.	DO.	86 MINS	228 mgms%	11.4° C	YES
7 14 KG.	METABOLIC 1.	25 C. 10 COLD 25 W.	60 MINS	78 mgms%	10.0° C	YES ^x
8 18 KG.	3 HR LOW PERFUSION 1	11 C. 180 LOW FLOW 38 W.	229 MINS	—	14.8° C	YES
9 18 KG.	METABOLIC 2.	24 C. 26 OFF 25 W.	49 MINS + 26 MINS OFF	—	11° C	YES
10 15 KG.	METABOLIC 3.	25 C. 10 COLD 25+ WARMING	60 MINS	100 mgms%	9.2° C	NO
11 18 KG.	METABOLIC 4.	25 C. 10 COLD 31 W.	66 MINS	176 mgms %	10.9° C	YES ^x
12 18 KG.	METABOLIC 5.	28 C. 7 C COLD 27 W.	62 MINS	4.72 mgms%	9.8° C	YES
13 15 KG.	RENAL 6 & LATE CONTROL	24 C. 15 COLD 38 W.	77 MINS	60 mgms%	11° C	YES

DOG NO. & WEIGHT	NATURE OF EXPERIMENT	BYPASS DETAILS IN MINS.	TOTAL DURATION OF BYPASS	PLASMA HB	LOWEST TEMP. IN OESOPH IN °C	SURVIVED 24 HRS. POST BYPASS
14. 17 KG.	RENAL 7	13 NORMO. 37 C. 8 COLD 31 W.	90 MINS.	87 mgs. %	92° C.	NO
15. 20 KG.	METABOLIC 6	25 C. 10 COLD 30 W.	65 MINS.	85 mgs. %	10.0° C	YES
16. 23 KG	METABOLIC 7	25 C. 10 COLD 26 C.	61 MINS.	76 mgs. %	13.8° C	YES
17. 14 KG	METABOLIC 8	25 C. 10 COLD 21+17 W.	56 + 17 MINS.	317 mgs. %	10.0° C	YES
18. 21 KG	TEMP. GRADIENTS 1	26 C. 12 COLD 24 W.	62 MINS.	16.9 mgs%	8.7° C	SACRIFICED
19. 17 KG.	TEMP. GRADIENTS 2	30 C. 8 COLD 30 W.	68 MINS.	—	10.5° C	SACRIFICED

FIGURE III, 4.

Results of the 19 experiments using profound hypothermia and the bubble oxygenator with dogs.

the technique, as well as to look for inherent dangers that might exist. Thus, in each experiment in the series using this combination, a study of some other factor was undertaken in addition to the study of the technique of the bypass itself. Long before the completion of the experimental series the technique appeared to be so satisfactory that its use was extended to some of the patients subjected to cardiac surgery in Cape Town. The experimental work was continued however, and further investigations are still in progress.

SECTION B - MATERIAL AND APPARATUS.

In this series, 19 healthy adult mongrel dogs, weighing between 14 and 23 kilograms, were used. The only selection employed was that the dog had to be apparently well on the morning of the operation. During the procedures, studies of renal and metabolic functions and other aspects, such as temperature gradients, were undertaken (Figure III, 4).

The donor blood used in the experiments was obtained on the morning of operation, and was kept at 40 degrees centigrade until used to prime the apparatus. The donor dogs were given "Flaxedil", intubated and intermittent positive pressure respiration, using nitrous oxide and oxygen, was instituted. A femoral artery was cannulated and the blood was run into previously heparinised glass bottles, which were agitated gently. Citrated blood was obtained in a similar manner. Barbiturates were not used in anaesthetising the donor dogs as this could have lowered the survival rate of the dogs used during the experiments (DeWall et al, 1957, a).

The cardio- /....

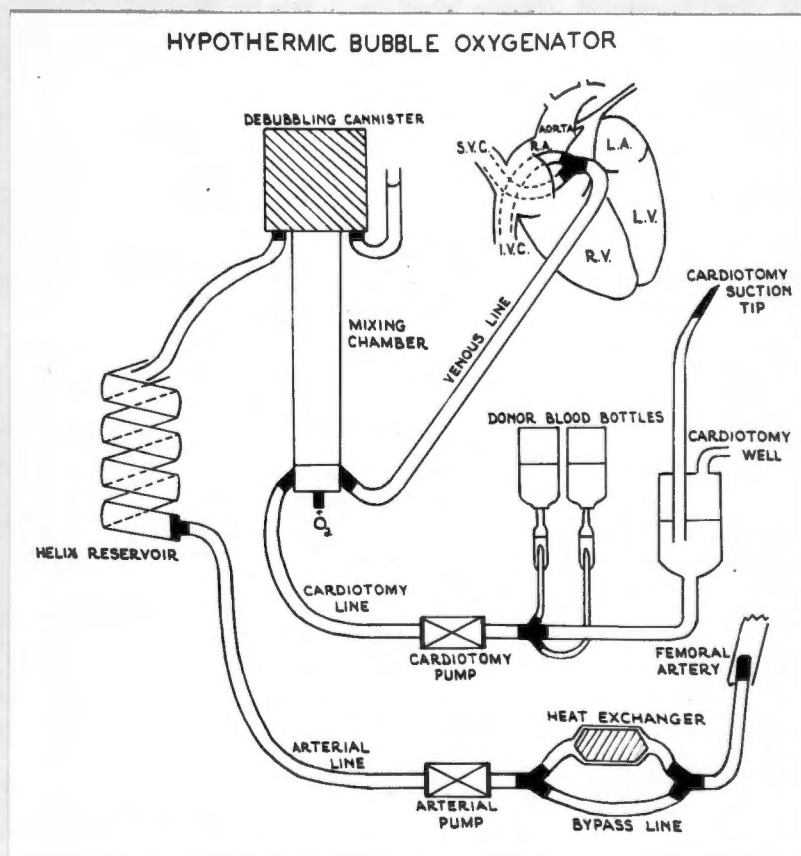


FIGURE III, 5.

A diagrammatic representation of the DeWall/Lillehei Helix Reservoir bubble oxygenator system as it is used for profound hypothermic perfusions in Cape Town.

The cardiopulmonary bypass apparatus used was the DeWall-Lillehei bubble oxygenator, as utilised now for normothermic perfusions (Figure III, 1), but with the addition of one or two Bennington heat exchange units in the arterial line. Figure III, 5, is a diagrammatic representation of the hypothermic circuit. The venous blood is drained by means of gravity, is oxygenated, debubbled and then passes into the helix reservoir. As the dog's temperature is controlled by means of the heat exchanger, the helix is not immersed in a water-bath (cf. Figure III, 1). The oxygenated blood is pumped by the arterial pump through the heat exchanger, where it is cooled or warmed, and then back into the dog's femoral artery. A line bypassing the heat exchanger is also incorporated in the arterial line, in order to keep the dog's temperature constant at any desired level and to facilitate the changeover from cold to warm water, when so desired. Although the diagram shows both the superior and inferior vena cavae cannulated, in dogs a single venous catheter is placed in the right atrium.

Figure III, 6, shows the bypass apparatus set up and ready to use for a perfusion. In the centre is the mixing chamber and the debubbling cannister, and on the left is the helix. In the right background are the heat exchangers, and the ice water tank is situated next to the oxygen cylinder.

Figure III, 7, shows two Bennington heat exchange units.* On the right is an assembled unit and the various components, prior to assembly, can be seen on the left. This heat exchange unit has been used in all the experiments in this series. It works on the principle that blood entering it through the nozzle at one end is spread in a thin film over the highly polished inner component, and so comes into contact with the similarly polished inner wall of the jacket carrying the heat exchange fluid, thus providing a highly efficient system of

heat /....

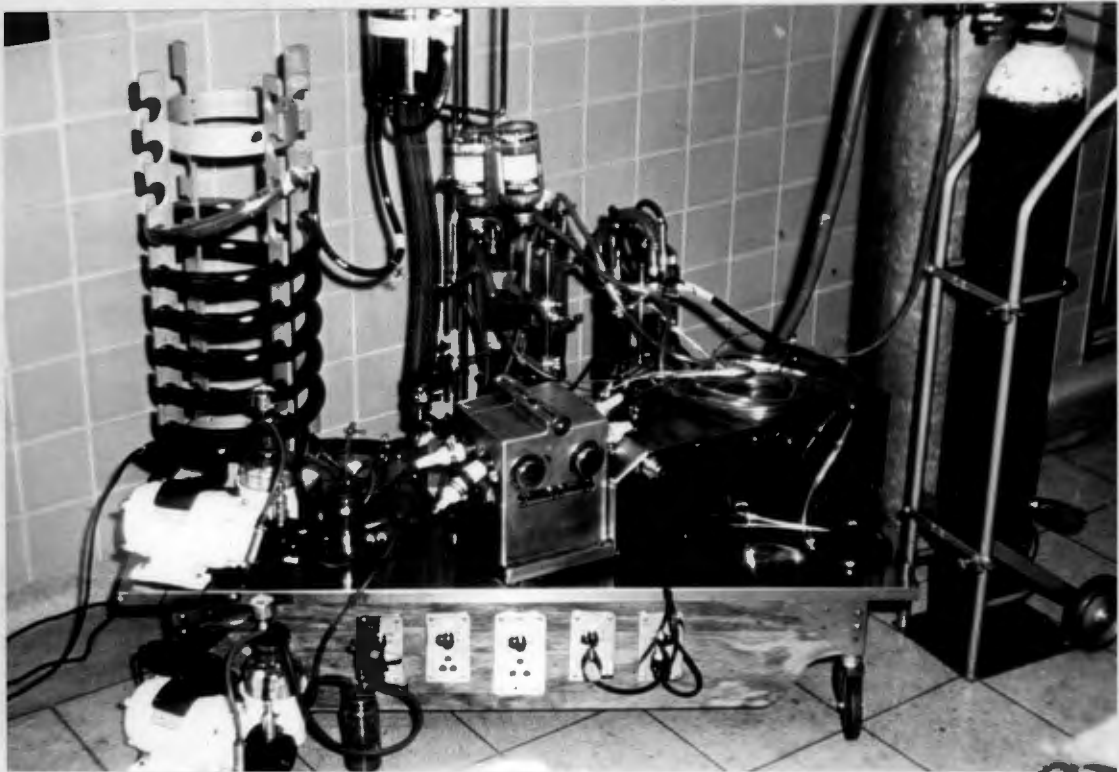


FIGURE III, 6.

**The assembled DeWall/Lillehei Helix Reservoir
bubble oxygenator system, as it is used for
profound hypothermic perfusions in Cape Town.**

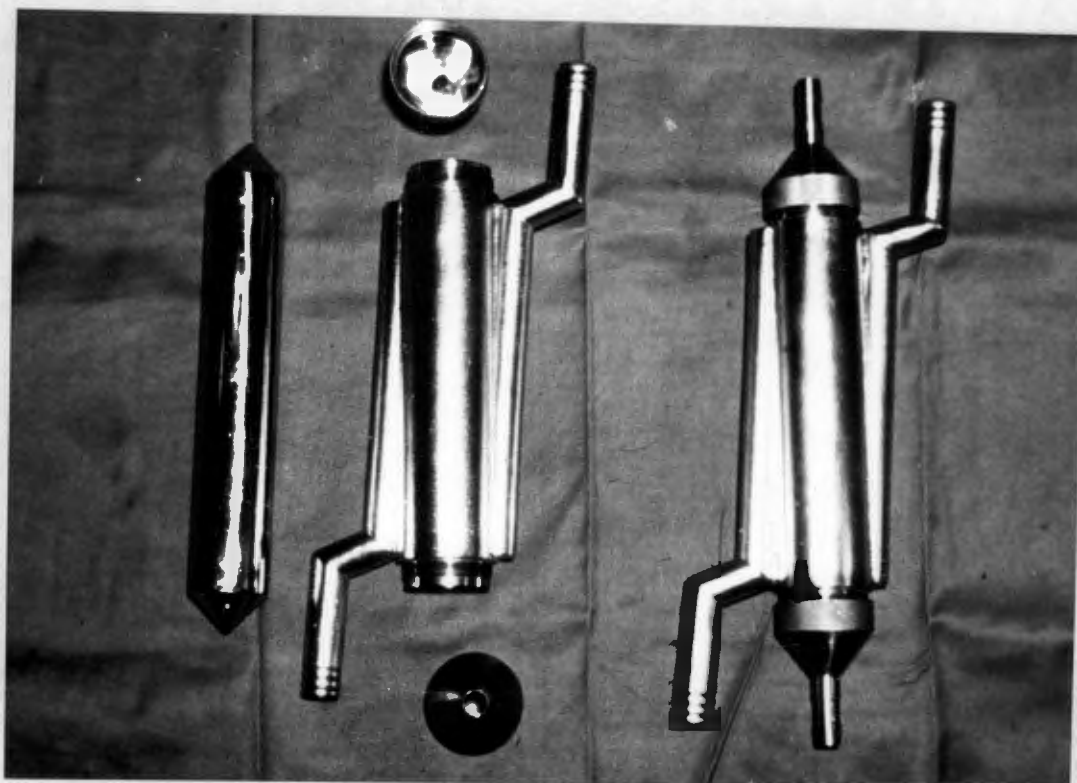


FIGURE III, 7.

Two Bennington Heat Exchange Units. The one on the right is assembled; that on the left is shown prior to assembly to show the various components.

heat exchange. Water from a tank containing melting ice is used for cooling, and water between 40 and 45 degrees centigrade for rewarming. This water is pumped from its tank through the heat exchange unit by an ordinary water pump which is regulated to give a flow of up to 12 gallons per minute. Figure III, 8, shows a single heat exchanger set up ready for use in a bypass. The water tank is situated on the left, and the water pump is in the bottom left-hand corner. As this heat exchange unit has a very low priming blood volume, 55 cubic centimetres, which is only a little more than would be contained in a similar length of 3/8 inch diameter Mayon tubing, its inclusion directly in the arterial line does not constitute a problem from this aspect.

During the experiments temperatures were recorded at various sites, using the Electric Universal Thermometer type TE3 with leads types R-7, O3G-1, K-8 and K-3, and connection box type FE10²s (see Figure III, 9). This is a precision thermometer operating on the thermocouple principle. It reads almost instantaneously and has an accuracy of 0.1 degrees centigrade.

The maintenance of anaesthesia in all cases was by intermittent positive pressure respiration, utilising a standard Boyles anaesthetic machine, delivering nitrous oxide and oxygen, or oxygen alone, through a cuffed endotracheal tube without the addition of a carbon dioxide absorber in the circuit.

Blood pressure and venous pressure was determined by using standard U-tube manometers connected to the femoral artery and femoral vein respectively (Figure III, 10). The manometers

were /....

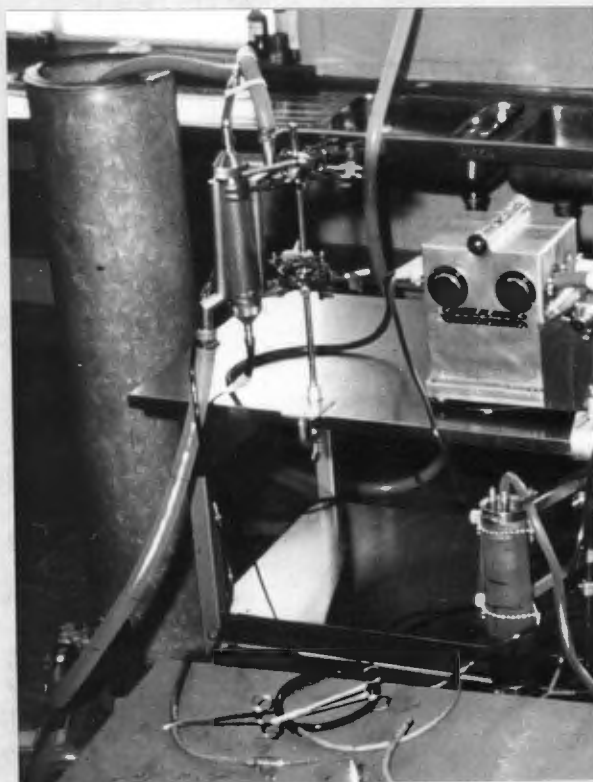


FIGURE III, 8.

**The assembled Bennington Heat
Exchanger, water tank and
water pump.**



FIGURE III, 9.

The Electric Universal Thermometer. Various leads, attached to the connection box, can be seen in the foreground of this picture.



FIGURE III, 10.

The U-tube manometers used for estimating arterial and venous pressures. On the right is the mercury manometer for arterial pressures, and on the left is the water manometer for venous pressures.

were adjusted so that they were situated at the same level as the dog's right auricle. By the time this series was begun, continuous E.C.G. and blood pressure were no longer recorded on a Sanborn apparatus, as sufficient information had been obtained from its use in previous experiments.

- * Supplied by Messrs, Westdene Products (Pty) Ltd., Cape Town.
- ** Manufactured by Elektrolaboratoriet, Copenhagen, Denmark.

SECTION C - METHODS.

(1) The Preparation of the Bypass Apparatus:

The preliminary preparation of the apparatus and its sterilisation by autoclaving is similar to that previously described in a Cape Town report for normothermic perfusions (Barnard et al, 1960; McKenzie and Barnard, 1958), with a few noteworthy exceptions. In the normothermic perfusions gravity drainage and a new debubbling cannister are used, now. The gravity drainage base of the mixing chamber is assembled prior to being autoclaved or boiled with the metal connectors. The new debubbling cannister*, which has a built-in nylon gravity filter, is also completely assembled and then autoclaved. The only additional requirement in these hypothermic perfusions is the heat exchange unit. This is completely assembled, but the ends are not tightly secured, and the unit is then autoclaved with the rest of the apparatus. Prior to use, the two ends are tightly screwed.

On the morning of the experiment, the autoclaved equipment is assembled under sterile conditions by a technician, and one or two heat exchange units are included in the arterial line.

A line bypassing the heat exchanger is also included (see Figure III, 5). The ice water tank is connected via the water pump to the heat exchange unit (Figure III, 8). If more than one unit is used, they are connected so that the blood flows through them in parallel, and the heat exchange fluid flows through the outer jackets in series. Once the apparatus has been completely assembled and is in place on the trolley (Figure III, 6), it is initially primed by pouring hot saline into the helix to dispel all the air (McKenzie and Barnard, 1958). When the debubbling of the oxygenator is complete, all air bubbles are dislodged and removed from the heat exchangers by pumping the hot saline through them at a very high flow rate. Calibration of the arterial pump and pump occlusion are then carried out as described before (McKenzie and Barnard, 1960).

When the dog's heart is exposed, and all the above described procedures are completed, the donor blood is pumped slowly by the cardiotomy pump from a blood bottle into the mixing chamber, where it is mixed with 100% oxygen. The flow of oxygen is so regulated that the bubbles just rise in this chamber. The blood is then debubbled and a stream of blood trickles gently into the helix, causing no turbulence and hence no bubbles form on the blood surface within the helix.

The preparation of the apparatus is now complete and it is ready to be connected to the dog.

(2) The Operative and Bypass Procedures:

The procedure to be described is the one that was used for almost all these dog bypasses. It has been evolved on the basis of the earlier experimental work on profound hypothermia. Special additional procedures, which were undertaken in certain experiments, will be discussed later in the relevant sections.

Basically /.....

Basically, the procedure is to cool the dog on bypass for a period of about 25 minutes. Cooling is then discontinued, while maintaining full flow bypass, and the dog is subsequently rewarmed. As most of the experiments were aimed at the study of certain special aspects, such as metabolic and renal function, no cardiac surgery was performed. The bypass is then discontinued and blood loss is replaced.

The usual method, in a little more detail, is as follows. The dog is anaesthetised with intravenous thiopentone sodium and is then intubated, using a cuffed endotracheal tube. Subsequent anaesthesia is maintained with nitrous oxide and oxygen alone, and additional thiopentone sodium is only given when absolutely necessary, as it is best to have the dog in as light a plane of anaesthesia as possible when the bypass is commenced. A slow intravenous drip infusion of 5 percent dextrose in water is set up in a forelimb. The dog is positioned on its right side, both groins being exposed by opening its legs and securing them in this position. An oesophageal temperature electrode (type OSG-1) is inserted to lie in the lower mid-oesophageal area, and the rectal temperature lead (type R-7) is inserted approximately $2\frac{1}{2}$ inches into the rectum. The dog's skin is prepared and the drapes are placed in position.

The operative procedure is commenced by performing bilateral femoral cutdowns. The left femoral artery and vein are cannulated and connected to the U-tube manometers, to record arterial and venous pressures respectively, during the procedure. The right femoral artery, which will later be connected to the arterial line of the apparatus, is dissected free. After this, the groin area is covered with a sterile towel.

The next /....

The next step is the opening of the thoracic cavity. A thoracotomy through the 4th left intercostal space is performed. Particular attention is paid to complete haemostasis, which is attained by means of coagulating diathermy. To obtain a good exposure of the heart, the pericardium is widely opened (Fig. III, 11). The situation of the oesophageal temperature electrode is checked to ascertain that it is in the correct position. The dog is heparinised, using 1.5 mgs. of heparin per kilogram of body-weight. The groin area is exposed again and the right common femoral artery is encircled with a cotton tape. The largest possible metal arterial catheter is inserted in a retrograde fashion into the artery for about 2 inches, and secured in position.

At this stage, the priming of the bypass apparatus with donor blood is already complete. Two needle temperature electrodes (types K-3 or K-8) are inserted into the arterial line Mayon tubing, so that they are situated in the blood stream, one on each side of the heat exchange unit. One end of a sterile Mayon tubing arterio-venous line is handed out from the table to the pump technician, who connects it to his end of the arterial line. The excess saline present is pumped out of the bypass apparatus, until whole blood fills the arterio-venous line completely. The filled venous portion of this line is clamped at either end, and disconnected from the arterial portion. One side is handed out to the pump technician who connects it to the bottom of the mixing chamber. The cardiotomy line is also handed out and is connected to the cardiotomy well.



FIGURE III, 11.

The heart exposed via a left thoracotomy. The left auricular appendage is at the top, slightly overlapping the pulmonary artery. The tip of the right auricular appendage is visible on the left.

The stage is set to connect the dog to the bypass machine. The connection of the femoral arterial catheter to the arterial line of the apparatus is performed in such a way so as not to introduce any air into the line. In the left thoracotomy approach, which is used, the tip of the right auricular appendage can just be seen (Figure III, 11). It is gently lifted, using a pair of fine forceps, and a purse-string suture of "0" silk is placed round its base. An auricular clamp, or some other clamp, is placed beneath the purse-string and an incision is made in the top of the appendage. A single No. 32 Bardic venous catheter is inserted through this appendage, into the cavity of the right atrium, and secured in position with the pursestring suture. It is then connected to the venous line of the apparatus.

The line bypassing the heat exchanger is clamped so that the blood will flow through the heat exchange unit. The water pump is switched on, thereby circulating cold water through the heat exchanger's outer jacket. The clamps on the arterial and venous lines are removed, and bypass is commenced by switching on the arterial pump. This has been calibrated to give a flow of 70 cubic centimetres per kilogram of body-weight, and the perfusion is commenced at this fairly high flow rate. Thus high flow, partial bypass and cooling are all commenced simultaneously. (The only exceptions were some of the dogs in which renal functions were studied, where cooling was not commenced at the beginning of the perfusion). As there is only a single catheter in the right atrium, the bypass naturally remains partial until ventricular fibrillation sets in.

As cooling /....



FIGURE III, 12.

**The heart exposed via a left thoracotomy.
II. Both right and left auricular appendages
have been cannulated with Bardic catheters.**

As cooling progresses, the heart begins to fail and ventricular fibrillation invariably occurs. At this stage, the left atrial appendage is cannulated in a similar manner to the right, and it is connected to the cardiotomy suction well. This provides left heart decompression during the period of ventricular fibrillation. In Figure III, 12, both the left and the right atrial catheters can be seen in place during an actual bypass. As a cardiotomy is not performed during these experiments, a second cardiotomy suction line is not necessary. During this phase, the high flow rate perfusion is maintained, and cooling is allowed to proceed until an adequate degree of profound hypothermia is produced.

Once the temperature is low enough, active cooling is discontinued by allowing the blood to bypass the heat exchangers, through the special bypass line included in the circuit. Thus the dog enters a "static" phase, with regard to its temperature. During this "static" period, the dogs do warm up slightly as there is no active cooling and the room temperature is well above the dog's temperature. The high flow rates are maintained (except in 4 of the experiments) and this time, usually about 10 minutes, is utilized to change the heat exchange fluid in the water tank. The iced water is drained out of the water tank and the pieces of ice which remain are removed. The tank is then filled with water which is at a temperature of between 40 and 45 degrees centigrade.

Rewarming is commenced by redirecting the blood through the heat exchanger, still maintaining a high flow rate.

During this period, in the earlier experiments, an arbitrary dose of 20 to 30 cubic centimetres of 4 percent sodium bicarbonate was given, to counteract any metabolic acidosis present, but none was administered during the later experiments.

When the mid-oesophageal temperature reaches 32 to 36 degrees centigrade, if spontaneous reversion to sinus rhythm does not occur, electric shock defibrillation is employed and is usually easily accomplished. Immediately the heart has reverted to sinus rhythm, left atrial drainage is discontinued and the catheter is removed soon afterwards. Once sinus rhythm commences, the cardiopulmonary bypass - which is complete while ventricular fibrillation is present - becomes a partial bypass once again. At this stage, when the heart beat appears to be satisfactory and the dog's temperature is high enough, the cardiopulmonary bypass is switched off.

The status of the dog's blood balance is estimated using the arterial and venous pressures as monitors, in preference to an estimation of the actual blood loss, and any blood deficit is immediately replaced via the arterial catheter. In the rare cases where the blood pressure is not maintained despite adequate blood replacement, adrenaline (1 in 100,000 solution) is administered slowly intravenously, usually with a good result. The first half of the required dose of protamine sulphate is given at this stage to neutralise the heparin. The catheter is removed from the right atrium, and the previously placed purse-string suture is securely tied. An additional ligature is tied around the appendage.

The pericardium is loosely approximated. A chest drain is inserted through a stab-wound lower in the thoracic cage, and is connected to a suction apparatus. The entire thoracic cavity and chest wound are inspected for bleeding. The thoracotomy is carefully closed in layers. All the femoral catheters are removed, the femoral vein is tied and the arteries are either tied or repaired with 6-0 black silk sutures. The femoral wounds are then closed. By this time

the /....

the second half of the required dose of protamine sulphate has already been administered.

Certain points arising out of the description of the operative and bypass procedures require further clarification at this point. As has already been mentioned, no cardiac surgery was performed during any of these experiments. The reason was that only a study of the effects of cardiopulmonary bypass in association with profound hypothermia, on various parameters, was the aim. For the same reason, most of the dogs were merely cooled and then rewarmed very soon afterwards. In all the experiments, with the exception of four, which will be discussed later, high flow rates of 70 cubic centimetres per kilogram of body-weight per minute were maintained throughout. This was done despite the fact that reports in the literature, and the author's previous work, indicated that complete cessation of circulation, or a low flow rate, was all that was required when profound hypothermia was utilised with cardiopulmonary bypass during cardiac surgery on patients.

The reasons for this were twofold: firstly, the preliminary investigations had shown that cooling and warming were achieved more rapidly when high flow rates were maintained; secondly, for a number of reasons, the aim was to maintain a uniform set of circumstances throughout these experiments, so that it would be possible to study the effect of adding profound hypothermia to a cardiopulmonary bypass without a further variable in the form of a low flow rate. Furthermore, only a left thoracotomy was used. The right atrium could be cannulated via its appendage, from this side, while left heart

decompression /....

decompression was easily performed. The preliminary investigations too led to the belief that dogs stand a unilateral thoracotomy better than they do a bilateral one. This approach, however, only permitted the insertion of a single catheter into the right atrium, and the venae cavae were not taped. Thus, the bypass remained partial until ventricular fibrillation set in, and was again partial when sinus rhythm was resumed after rewarming. In the patients, however, a complete cardiopulmonary bypass was usually utilised throughout the procedure (see Chapter Four).

(3) The Postoperative Period:

After the completion of the operative procedure, the dog is returned to a warmed recovery cage. Unlike the patients, they receive no special postoperative care. Obvious blood loss, which accumulates in the chest drainage bottle during the hours immediately postoperatively, is replaced volume for volume with citrated blood. They are given an intravenous infusion of about 500 cubic centimetres of 5 percent dextrose in water containing about 30 cubic centimetres of 4 percent sodium bicarbonate solution, overnight. Antibiotic therapy is routinely instituted with 2 to 4 million units of penicillin and $3/4$ to 1 gram of chloramycetin, administered in divided doses, daily, for the first postoperative week. The chest drainage tube is removed, either on the night of the experiment or on the following morning. The dogs are maintained on intravenous fluids for the first postoperative day, the intravenous drip is then taken down and thereafter they are offered the standard laboratory diet.

The dogs are carefully observed after 24 hours and are examined again after a week. The long-term survivors (those which are well at the end of the first week) are sent

away to kennels and some of them are used later as donors for further experiments.

(4) Biochemical Estimations:

The details of the techniques used in the special investigations carried out will be described later in the relevant sections.

The plasma haemoglobin level, an estimate of blood destruction, was estimated routinely at the end of each procedure by the method described by Crosby (Crosby and Furth, 1956).

SECTION D - GENERAL RESULTS AND DISCUSSION:

In this section the general results of the whole group will be dealt with and discussed. Some of the results obtained in the 19 dogs which constitute this series are tabulated in Figure III, 4. The nature of the various experiments is indicated and the details of the bypass itself is briefly summarised. It can be seen that, in most cases, the bypasses were performed as described in Section C - Methods.

(1) Variations in Technique:

In 4 of the experiments, a marked variation in technique from that described in Section C occurred. The circulation in dog No. 9 had to be completely arrested, when it was cold, due to a technical hitch. The dog was subsequently rewarmed, using autogenous oxygenation (Terblanche and Barnard, 1960). In dog No. 2, instead of maintaining the bypass when the desired temperature had been attained, the circulation and respiration were stopped completely for 30 minutes. After rearming, the dog returned to normal.

These experiments add confirmation to the previous findings that a dog can survive a period of up to 1 hour of circulatory arrest during profound hypothermia (Terblanche and Barnard, 1960).

In dog No. 8, the effect of a prolonged bypass, with a low flow rate, was studied.

Dog No. 1 constituted an interesting, separate acute experiment in which the effect of prolonged circulatory arrest at very low temperatures was tested. The dog was cooled to 6.9 degrees centigrade and its blood was then drained and replaced with "Dextran". The dog was then kept in a refrigerator overnight at 4 to 6 degrees centigrade. The following day it was placed on the operating table, the "Dextran" was replaced with heparinized blood and rewarmed, on cardiopulmonary bypass, was commenced. Some tone returned to the heart, in spite of a period of 18 to 20 hours with no circulation. Unfortunately, despite energetic measures, no heart beat could be obtained. During rewarming it was also noted that the size of the dog's pupils varied at different stages. These observations indicated that some degree of viability of tissue had persisted. The experiment was discontinued at this stage and the dog was sacrificed.

Thus the protection afforded the vital organs and other tissues by profound hypothermia, for a limited time, does not continue indefinitely. When the period of circulatory occlusion is too prolonged, irreversible damage occurs in some tissues despite the presence of profound hypothermia. This constitutes another indication of the

importance /....

importance of multiple and detailed studies during profound hypothermia, to give a fuller understanding of its action on the organism and a clearer idea of the maximum period of its safe application, thereby rendering its clinical use more safe.

(2) Length of the Perfusions:

The average length of time of cardiopulmonary bypass (excluding dog No. 1) was 80 minutes, and in only one of the experiments did it last for a total period of less than an hour. These long perfusions, however, did not seem to affect the survival rate - despite the fact that normothermic bypasses of much longer than an hour in dogs are very often fatal (Sanger et al, 1960). For instance, dog No. 8 was cooled and then perfused at a low flow rate for a period of three hours, and it is interesting to note that this dog was one of the long-term survivors, in spite of having been on bypass for 229 minutes.

Thus a prolonged perfusion is feasible in the profoundly hypothermic dog, when the animal is protected by even a low flow rate, to meet any metabolic requirements that may be present. This demonstrates clearly the increased safety afforded a cardiopulmonary bypass by the addition of profound hypothermia.

(3) Blood Destruction:

In this series, the postoperative plasma haemoglobin figures (a measure of the blood destruction in the apparatus), which averaged 106 mgs. percent, were on the whole nowhere nearly as low as in a previous series of experiments on dogs in which autogenous oxygenation was used (Terblanche and Barnard, 1960).

This relatively high degree of blood destruction is felt to be related to the bubble oxygenator itself, and it may well be a point against the use of this oxygenator in such a system. In none of the cases, however, was the level sufficiently high to really endanger the dog's life (except possibly dog No. 17). When the results of the "metabolic dogs" are presented, this question of blood destruction will again be dealt with (see Section G).

(4) Temperatures:

The lowest esophageal temperatures reached were all in the lower ranges of profound hypothermia, in the vicinity of 10 degrees centigrade.

The ease with which these temperatures are attained demonstrates the efficiency of the system of heat exchange used. A more detailed assessment of the temperatures will be made in a later section (see Section E).

(5) Survival:

Two of the 19 dogs in this series had needle electrodes placed in their brains, and were sacrificed at the end of the procedure. They will thus be excluded from this discussion of the survival rate.

- (a) Immediate Survival: In the 17 remaining dogs, only 5 (29.4 percent) failed to survive the procedure. The other 12 dogs (70.6 percent) made a complete recovery from the perfusion and after 24 hours were still well.

The first dog's death was understandable as it was kept cold with no circulation for 18 to 20 hours.

Dog No. 5 died on the table, as a result of uncontrollable bleeding. The cause was only later traced to a substance, with a heparin-like action, which was present in the P.A.H. used in testing the dog's renal function. Dog No. 10's death was due to a technical error during surgery, whereby a large amount of air was introduced into the coronary arteries. Dog No. 14 recovered from the perfusion completely but was found dead the following morning. Postmortem examination revealed a large collection of blood in the left chest. This dog would have been a survivor, probably, had the immediate post-operative care been better. Dog No. 17 died as a result of air embolism due to a faulty bypass during rewarming, when air was allowed to enter the dog from the bypass apparatus.

Thus, of the immediate deaths, only one (Dog No. 1) is directly attributable to the technique of profound hypothermia, a definitely unrelated cause of death being present in the others. This 70.6 per cent immediate survival rate confirms the opinion that profound hypothermia is safe, and that dogs return to normal pre-operative conditions almost immediately after rewarming (Terblanche and Barnard, 1960).

(b) Long-term Survival: Of the 12 dogs that were well 24 hours postoperatively, 7 were long-term survivors (i.e. they were well when examined at the end of one week). Four of the others died

of /....

of severe anaemia, due to haemorrhage (including the first three "renal function dogs", probably due to the P.A.H. used), and the fifth dog died of gross infection. These five dogs are marked with crosses in the survival column in Figure III, 4. All these deaths occurred in the first postoperative week.

Once again, with adequate postoperative care, at least some of these later deaths could probably have been avoided. There is, however, no doubt that they are not attributable to the use of profound hypothermia per se.

This overall survival rate is felt to be good, particularly bearing in mind the fact that dogs stand cardiac bypass notoriously badly (Sanger et al, 1960). The important point that arises is the fact that many dogs survive and are well after such a procedure, and that the deaths in those which did not survive were due to some factor unrelated to the technique of profound hypothermia. Another important point which confirms the findings of Sealy (Sealy et al, 1958, b; 1959; Lesage et al, 1959), and others (Gollan, 1959; Urschel et al, 1960; Gerbode et al, 1960, a), is that oxygen bubbles and oxygen embolism do not occur, despite the fact that the heat exchange unit is included in the arterial line during the rewarming phase, without a bubble trap.

(6) The Heart:

The blood and venous pressure variations will be dealt with in a later section (see Section 6).

The rate and rhythm of the heart was observed to undergo the following changes. During cooling there was an initial slowing of the heart rate, but ventricular fibrillation

usually /....

usually ensued as the mid-oesophageal temperature passed the twenties. At lower temperatures the ventricular fibrillation became sluggish. During the static period myocardial activity either ceased altogether or a very slow and sluggish ventricular fibrillation persisted.

On rewarming, events occurred in reverse order. At the commencement of rewarming, myocardial activity was usually in the form of a slow fibrillation which became more vigorous as the myocardial temperature rose. Spontaneous sinus rhythm occurred at temperatures ranging from 14.7 to 35.4 degrees centigrade in 5 of the dogs. In the remainder electric shock defibrillation was required, but only an average of 2 shocks of 135 volts for 0.1 of a second, with a maximum of 6 shocks, were necessary before the heart returned to sinus rhythm. In 4 of the cases, the heart's action at this stage was not satisfactory, and a slow infusion of 1 in 100,000 solution of adrenalin was necessary to obtain a satisfactory beat. No other cardiac stimulant drugs were used in any of the dogs, except in Dog No. 1.

Although this type of hypothermia produces ventricular fibrillation or cardiac arrest, it is easily reversible after the procedure. When ventricular fibrillation is present, the dog's circulation is taken over by the cardiopulmonary bypass. Thus, unlike hypothermia produced by surface cooling, where ventricular fibrillation is feared, that produced in this way is an advantage because it helps to produce a quiet heart. The slowing that occurs, firstly in the sinus rhythm and subsequently in the ventricular fibrillation, is an indication of the slowing

of all body processes, brought about by cold.

(7) Safety Factors Associated with this Technique:

It has already been pointed out that longer perfusions become safe in the presence of profound hypothermia. Dog No. 9 illustrated well an important point in favour of the use of hypothermia with cardiac bypass. When this dog's temperature was in the low ranges, a technical hitch occurred with the bypass apparatus, and it was possible to halt the circulation completely for 26 minutes while the necessary adjustments were being made to continue the bypass and rewarm the dog with autogenous oxygenation. This dog was a long-term survivor, but had this mishap occurred under normothermic conditions, it would probably have proved fatal.

This added protection should always be borne in mind when deciding whether to use an ordinary cardiopulmonary bypass, or bypass with hypothermia, for a particular perfusion. With the added safety margin provided by hypothermia, one is prepared to meet most eventualities and even a complete power failure need not be a major hazard.

(8) Conclusions:

(a) Dogs are able to survive without a circulation for a limited period of time when they are protected with profound hypothermia. This protection does not remain complete indefinitely though, which indicates the necessity for detailed study during profound hypothermia to determine the length of time it may safely be applied.

(b) /

(b) When profound hypothermia is added to a cardiopulmonary bypass, the perfusion may be continued for a much longer period of time, with safety.

(c) The possibility that some other oxygenator should be used in preference to the bubble oxygenator, when inducing profound hypothermia, is indicated by the high haemolysis which occurs when the bubble oxygenator is utilised.

(d) The system of heat exchange used is efficient. This is evidenced by the ease with which low temperatures are attained.

(e) The technique described is safe, and dogs return to pre-operative conditions almost immediately after rewarming. This is indicated by the good immediate, and long-term, survival rate, and by the fact that the causes of death, where it occurred, was not attributable to the profound hypothermia. The one exception was when the circulation was stopped completely for many hours.

(f) Oxygen embolism is not a problem, despite the fact that the heat exchange unit is included in the arterial line of the system, without a bubble trap, during rewarming.

(g) The ventricular fibrillation that occurs is not a danger but is an advantage, and is easily reversed.

(h) A slowing of body processes occurs during profound hypothermia. An indication of this is the initial slowing of the heart rate and the subsequent slowing of ventricular fibrillation.

(i) Profound hypothermia adds a safety margin to cardiopulmonary bypass, as even the failure of the apparatus or of power can be dealt with, while the circulation is stopped, without danger to the dog.

SECTION E - TEMPERATURE GRADIENTS OCCURRING DURING
PROFOUND HYPOTHERMIA WITH THE BUBBLE OXYGENATOR

It was Claude Bernard who observed that temperature determinations made in various vessels within the body cavity, at normal body temperature, show a definite variation from site to site (Bernard, 1876, b). This work lay dormant until Horvath confirmed it and stated that: "The temperature of the blood throughout the vascular system is not constant Marked thermal gradients were observed, not only in the peripheral blood, but also in the blood draining the organs of the body core" (Horvath, Rubin and Foltz, 1950).

It is not surprising that, during surface-induced hypothermia, these normal temperature gradients become greater. The blood, which has passed through the cold surface tissues, must necessarily be colder than that which has passed through the deeper tissues of the body. Cooper pointed out the importance of the recognition of the presence of these differences during hypothermia, as the important temperature to know is that of the vital organs, and not that of the body surface. He also emphasized the fallacy of the belief held by many regarding the efficiency of determining the deep temperatures by recording the oral or rectal temperature (Cooper, 1959). Severinghaus and Hercus both confirmed this in their experimental work, and concluded that the lower oesophageal temperature was the best guide to core temperature in surface-cooled animals. Hercus demonstrated specifically that the lower oesophagus shows the closest correlation to cerebral temperature (Hercus, Cohen and Bowering, 1959). Severinghaus was able

to show /...

to show that the temperature varied at different depths in the rectum, and pointed out that "of course, a thermometer, if surrounded by faecal matter, may respond sluggishly to rectal temperature changes" (Severinghaus, 1959; Stuppel and Severinghaus, 1956).

The creation of an internal temperature gradient is the basis of the success of inducing hypothermia via an extracorporeal circuit. Cold blood passes into the body, and thus those organs with the richest blood supply (and hence the greatest metabolic activity) cool the quickest. The great advantage of extracorporeal cooling with an oxygenator, therefore, is that the tissues with the highest consumption of oxygen are cooled the most quickly, and, on rewarmed, are supplied with adequate oxygen (Gollan, 1959). Early workers were aware of the thermal gradients produced during extracorporeal circulatory hypothermia (Peirce and Polley, 1953), and Gollan noted that only the temperatures of the vital organs (the heart and brain) and the oesophagus fell really low (Gollan et al, 1955, b). Subsequently it was found that the heart, liver and kidneys cooled the most quickly, the brain and oesophagus cooling only slightly more slowly (Brown, Smith, Young and Sealy, 1958, b). Kenyon also described the temperature gradients (Kenyon et al, 1959), and Shield found that the brain did not cool as rapidly as was expected, while the lowest temperature was recorded in the liver and the muscles cooled only to 32 degrees centigrade (Shields and Lewis, 1959). The importance of the comparison of the thermal gradients induced by various techniques led Emerson to propose the use of his "selective cooling /.....

cooling index" as a working index of the differential cooling noted with internal hypothermia (Emerson, Sebening and Neville, 1959).

Despite the abundant evidence that thermal gradients are produced in blood-stream hypothermia, the fallacy of the belief that temperatures such as rectal or oral are a guide to the vital organ temperature, is still not generally appreciated. As recently as 1960, a worker in the field of profound hypothermia published a report on his experimental observations (including one patient) in which the temperature recorded was the pharyngeal (Simpson, Gibson and Bloomfield, 1960).

During the course of the bypasses in the 19 dogs discussed in this chapter (see Figure III, 4), the oesophageal and rectal temperatures were observed in every case. In most experiments the temperatures of the blood leaving the dog, and that of the blood leaving the heat exchange unit, were also observed. In the last 2 dogs, temperatures were recorded at numerous other sites, as well, to determine the extent and type of thermal gradients which occur with this method of inducing profound hypothermia. In both dogs the brain temperature was recorded, it being important to show that this organ is adequately cooled with the technique.

Previously, during the course of earlier investigations which led to the development of the present technique, the low midesophageal temperature was demonstrated to be the closest to that of the vital organs, including the brain. This was later confirmed during the experiments using autogenous oxygenation (Terblanche and Barnard, 1960). Thus the oesophageal temperature lead in the dogs in this series was carefully positioned in the low midesophagus.

In /....

In this section, the temperature gradients which occurred during the experiments will be shortly discussed, paying particular attention to the last 2 dogs. The main reasons for separating this section from the rest of the work were to place stronger emphasis on the importance of temperature gradients and on the usefulness of the use of the low mid-oesophageal temperature as a guide to vital organ temperature. In addition, up to the time of writing, no specific separate report on the subject of temperature gradients during profound hypothermia with extracorporeal circulation had appeared in the literature.

(1) Material:

The temperature gradients which occurred in 4 of the 19 dogs in this series (Figure III, 4) will be discussed in detail. In dogs Nos. 18 and 19 numerous temperatures were taken, and dogs Nos. 15 and 17 have been selected as typical representatives of the other dogs. In addition, a graph of the temperatures recorded during the twelfth experiment in the series using autogenous oxygenation (Terblanche and Barnard, 1960) has been included for purposes of comparison.

(2) Methods:

In Sections B and C of this Chapter the details of the bypasses were described and the thermometer used to record the temperatures was discussed (Figure III, 9), as well as the usual insertion of the thermometer leads, as placed in dogs Nos. 15 and 17.

In dog No. 18 the temperatures in the oesophagus, rectum, blood entering the heat exchange unit, and in the blood entering the dog, were recorded as in the other experiments. The inferior /...

inferior vena caval blood temperature was recorded using a lead OSG-1 inserted into the inferior vena cava, via the right femoral vein. The posterior pericardial temperature was also recorded, using a lead OSG-1, inserted into the posterior pericardium behind the heart. The neck and left thigh muscle temperatures were recorded using needle electrode leads, K-8, inserted into these sites. To record the brain temperature, a small incision was made over the left side of the skull and a fairly large hole was drilled through the bone, using an ordinary hand-drill. A needle electrode, lead type K-8, was inserted into the substance of the left cerebral hemisphere until the base of the needle was situated at the level of the skin. Special sterile precautions were not taken at this stage, thus the dog was sacrificed at the end of the procedure.

In dog No. 19 the temperatures in the oesophagus, in the rectum, in the blood entering the heat exchange unit, in the blood entering the dog, in the inferior vena cava and in the brain, were recorded in exactly the same way as in dog No. 18.

(3) Results and Discussion:

Figures III, 13 to 16, present in graphic form the temperatures recorded at various sites in the dogs to be discussed. Figure III, 17, shows the temperatures obtained during the twelfth experiment in the previous series where autogenous oxygenation was used.

(a) Low Midoesophageal Temperature: In these graphs the close relationship between the low mid-oesophageal temperature and that of the vital organs and the blood draining from the body, is clearly shown. For example, in dog No. 18

(Figure III, 15), a very close relationship was observed between the temperatures in the oesophagus, the heart (posterior pericardial) the blood draining from the dog and the blood in the inferior vena cava, throughout the bypass.

The relationship of oesophageal to brain temperatures will be discussed later. These observations are felt to confirm further the previous opinion that the "low midoesophageal temperature" is the "most easily recordable, and the most accurate guide to the temperatures of the vital organs" (Figure III, 17) (Terblanche and Barnard, 1960).

(b) Rectal Temperature: Two patterns of variation in rectal temperature occurred during the bypasses in the 19 dogs in this series.

The first was demonstrated by Dog No. 15 (Figure III, 13), where the rectal temperature lagged relatively far behind the oesophageal temperature - and hence the vital organ temperature - and only dropped to 22 degrees centigrade. During rewarms the rise was slow and the final temperature attained at the end of the perfusion was under 32 degrees centigrade. This pattern occurred in 9 of the 19 dogs.

The second pattern, in the remainder of the dogs, showed the fall and rise of rectal temperature following that of the low mid-

oesophagus /...

oesophagus much more closely, as demonstrated by dogs Nos. 17 and 19 (Figures III, 14 and 16). It did, however, lag behind the oesophageal temperature to some extent. A similar picture was found in some of the earlier experimental work (Figure III, 17).

The reason for the variation in rectal temperatures is not at all clear, but its presence emphasises well the fallacy of the belief that the rectal temperature can be used as a guide to vital organ temperature. It is possible that the rectal lead was not inserted to exactly the same depth in all the dogs, and that in some it was imbedded in faeces, which would account for the variation (Severinghaus, 1959).

(c) Brain Temperature: The temperature recorded in the brain in dog No. 19 (Figure III, 16) followed fairly closely that of the low mid-oesophagus. This was similar to the findings in the past (Figure III, 17). It tends to confirm the previous opinion that the brain temperature, like that of other vital organs, is accurately indicated by the temperature recorded in the low mid-oesophagus.

In dog No. 18 (Figure III, 15), however, the fall and rise was a little slower than was expected. It is interesting that the brain temperature in this dog corresponded more closely to the rectal temperature than to the oesophageal. (This was one of the dogs in

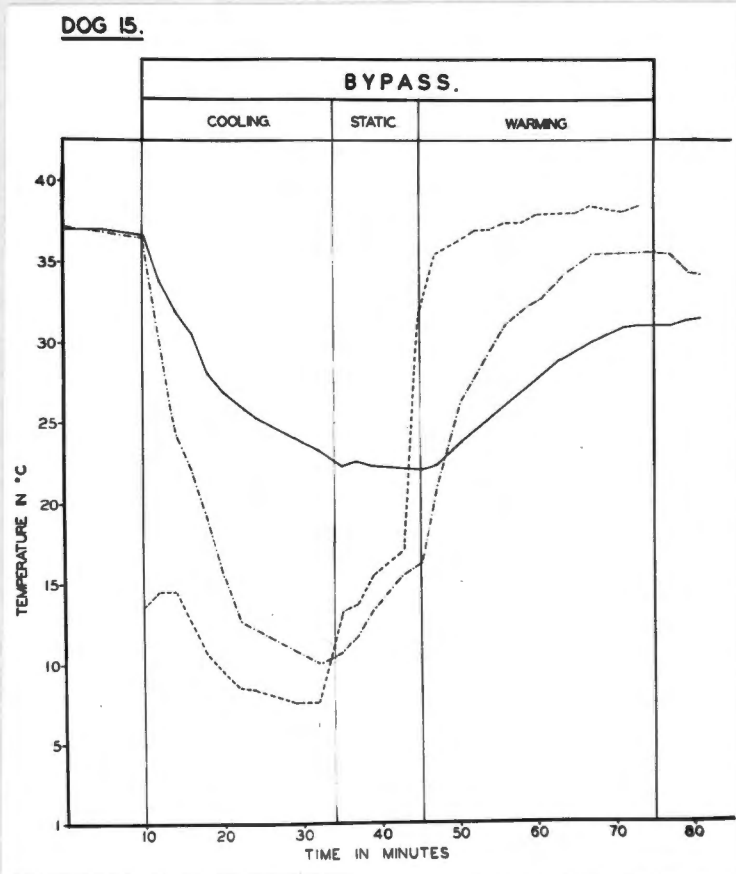


FIGURE III, 13.

Temperature gradients which occurred during the hypothermic perfusion of Dog No. 15. Rectal, esophageal and cooler temperatures are represented by lines similar to those used in Figure III, 14.

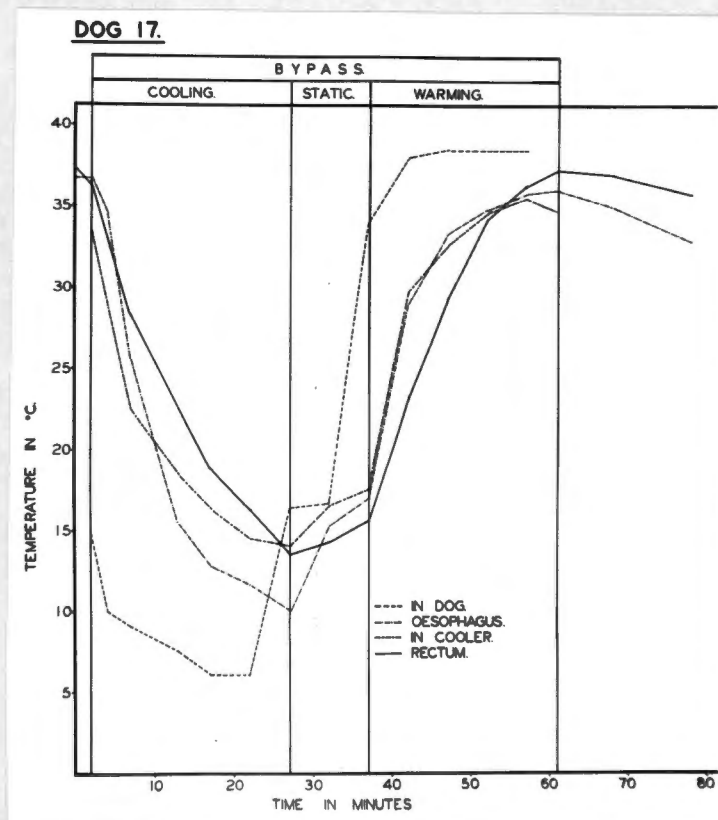


FIGURE III, 14.

Temperature gradients which occurred during the hypothermic perfusion of Dog No. 17.

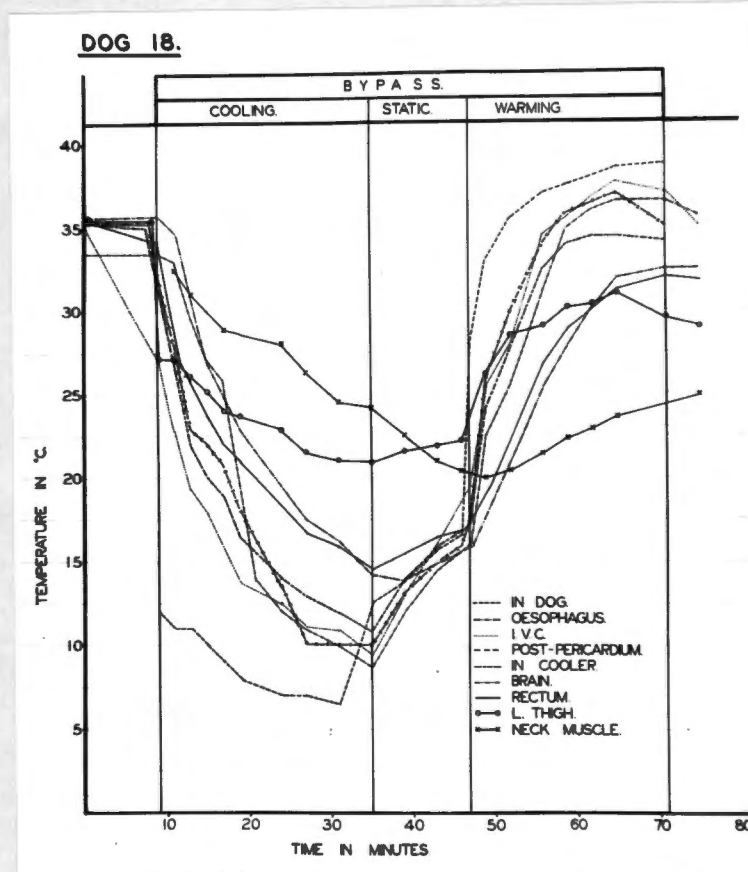


FIGURE III, 15.

Temperature gradients which occurred during the hypothermic perfusion of Dog No. 18.

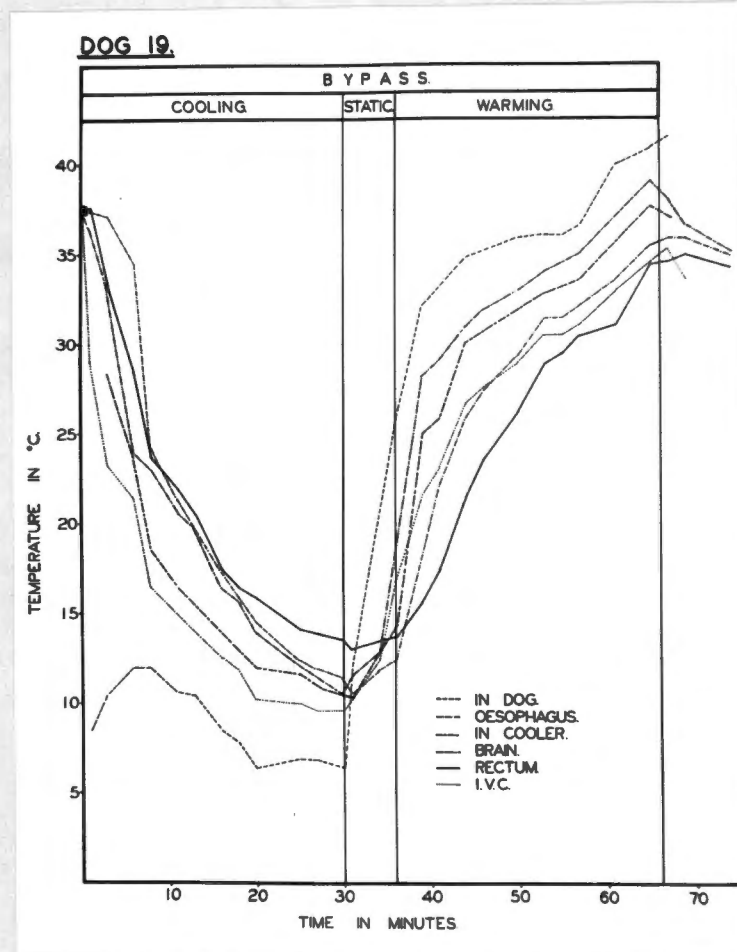


FIGURE III, 16.

Temperature gradients which occurred during the hypothermic perfusion of Dog No. 19.

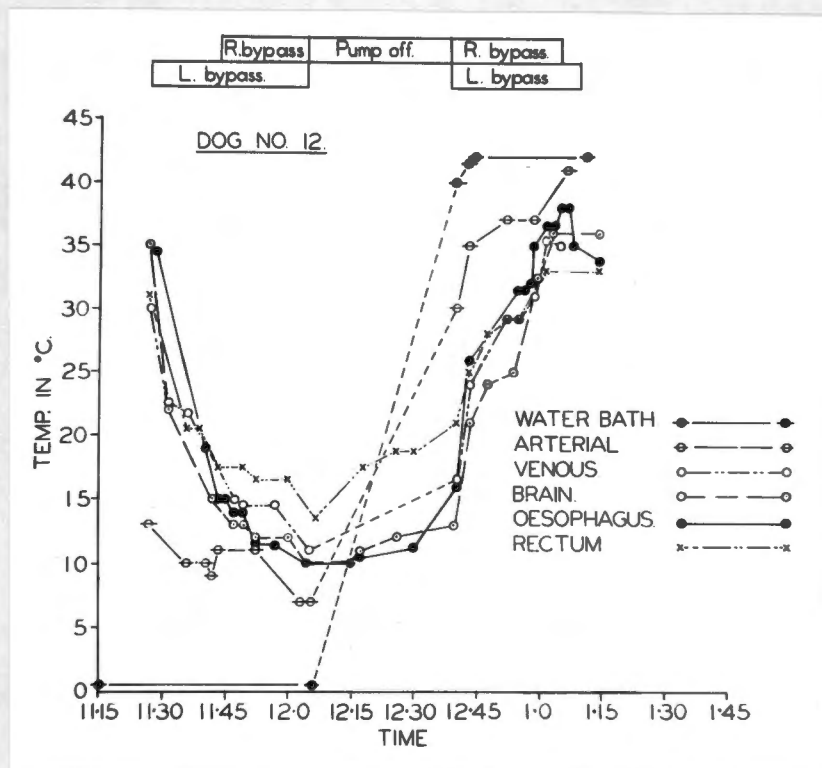


FIGURE III, 17.

Temperature gradients which occurred in Dog No. 12 of a previous series when autogenous oxygenation was used (Terblanche and Barnard, 1960). This graph has been included here for comparative purposes.

in which a marked fall in rectal temperature occurred).

Although the reason for this, again, is not clear, it is important to realise that it might occur. Thus, total cessation of circulation at a fairly high mid-oesophageal temperature for any length of time might be hazardous, should this delayed fall in brain temperature occur. This is another indication for maintaining at least a low flow of oxygenated blood throughout the course of a cardiopulmonary bypass with hypothermia, and for the use of the technique described in this chapter in preference to that described by Drew (Drew et al, 1959, a and b), and the author (Terblanche and Barnard, 1960).

(d) Posterior Pericardial Temperature: The variations that occurred in the posterior pericardial (and therefore in the heart) temperatures are shown in Figure III, 15. A very close correlation to the low mid-oesophageal temperature was observed. This again demonstrates the value of the mid-oesophageal temperature as a guide to the vital organ temperature.

(e) Inferior Vena Caval Blood Temperature: In dogs Nos. 18 and 19, this temperature correlated closely to that of the blood leaving the dogs. This indicates that the temperature of the blood in the lower half of the body was similar to that in the entire body. In both these cases the rectal temperature fell fairly low. It is possible that, in the dogs in which the rectal temperature did not fall so low, the inferior vena caval blood

from the lower half of the body was not as cool as that coming from the upper half of the body.

(2) Neck and Left Thigh Muscle Temperatures: A slow fall and rise occurred in these temperatures in dog No. 18 (Figure III, 15). This clearly illustrates the point that, during this method of hypothermia, the temperature of the non-vital organs lags well behind that of the vital organs.

A considerable "after drop" occurred in the neck muscle temperature. A similar "after drop" takes place in surface hypothermia, but it is the vital organs that continue to cool here (Sellick, 1960).

(4) Conclusions:

In this section, the temperature gradients that were observed in 4 dogs out of the total of 19 dogs subjected to this procedure, are discussed. They are also compared with the temperature gradients which occurred during an experiment in a previous series, using a different technique. In concluding, the important factors that have been brought to light will be reiterated.

- (a) The low mid-oesophageal temperature is a useful and sufficiently accurate guide to the vital organ temperature (i.e. heart and brain).
- (b) A wide variation occurs in the rectal temperature during this method of hypothermia. At times the rectal temperature corresponds fairly closely to the oesophageal temperature, but at other times it lags behind considerably. Possible explanations for this are put forward.

This /...

This variation, however, renders the rectal temperature a fallacious guide to the temperature of the vital organs.

- (c) The brain temperature is well indicated by the temperature in the low mid-oesophagus. The temperature of the brain may, however, be found to lag a little behind that of the oesophagus, and therefore total cessation of circulation for any length of time, at a fairly high mid-oesophageal temperature, may be dangerous. The perfusion of the body with oxygenated blood (even at "low flow" rates) during the hypothermic phase is therefore a safer procedure. This is a further indication for the use of the perfusion technique described in this chapter in preference to the autogenous oxygenation technique.
- (d) During this type of hypothermia, the temperature of the non-vital organs lags well behind the temperature of the vital organs. An "after drop" in temperature in the former tissues may occur after active cooling has been discontinued, in contradistinction to surface cooling where the "after drop" occurs in the vital organs.

SECTION F - RENAL FUNCTION STUDIES DURING AND IMMEDIATELY AFTER THE PROFOUND HYPOTHERMIC EXPERIMENTS.

The body's reaction to certain noxious influences is not always favourable and health-preserving. An example of this is seen in the dramatically sharp reduction in renal blood flow,

often /...

often to dangerously low levels, which frequently follows mild or moderate blood loss.

Surgical techniques employed for the improvement of operative conditions in certain organs may evoke responses in others which are perhaps detrimental, and a sound knowledge of such concomitant responses is essential. Only when it is clear that the beneficial effects of these techniques outweigh the dangerous effects can their use be justified.

In this study, the usefulness of profound hypothermia in improving operative conditions in the heart was investigated. It was felt to be important to determine whether the reactions evoked by this surgical technique in the kidney were detrimental. Thus, in this section, the changes which were noted in certain renal functions during and after profound hypothermia with a cardiopulmonary bypass will be discussed.

This section has been made a distinct part of this chapter to emphasise the changes that occur in renal function as, even today, despite the wealth of literature on profound hypothermia associated with extracorporeal circulation, no report of a study of renal function is available. This work is felt to fill an important gap in present-day knowledge.

(1) Material:

Ten healthy, adult, mongrel dogs, weighing between 15 and 21 kilograms, were included in this section (Figure III, 18). Seven of the 8 in which profound hypothermia was induced were also included in the general series (Figure III, 4). The material used was otherwise the same as that already described (Section B). The reason dog No. 10 was not included in the general series was that the experiment was performed after most of this thesis had been completed.

DOG NO. & WRIGHT.	EXPERIMENT	BYPASS DETAILS IN MINUTES.	TOTAL DURATION OF BYPASS IN MINUTES.	PLASMA Hb.	LOWEST OESOPH. TEMPERATURE ° C.	WELL 24 HRS. POST-BYPASS	RENAL FUNCTION STUDIED.
1 15 kg	Hypothermic Renal function	30 cooling 30 off 30 warming	60 + 30 off	-	11	Yes	Yes
2 21 kg	Hypothermic Renal function	Normo cooling static warming	106	54 mgs.%	9.3	Yes	Yes
3 17 kg	Hypothermic Renal function	10 normo 10 25°C 10 10°C warming	89	48 mgs.%	11	Yes	Yes
4 20 kg	Hypothermic Renal function	do.	71	112 mgs.%	10.2	No	Yes
5 17 kg	Hypothermic Renal function	do.	86	228 mgs.%	11.4	Yes	Yes
6 20 kg	Normothermic Renal function	30 normo	30	40 mgs.%	-	Yes	Yes
7 15 kg	Hypothermic Renal function	24 cooling 15 static 38 warming	77	60 mgs.%	11	Yes	No
8 16 kg	Normothermic Renal function	44 normo	44	35 mgs.%	-	Yes	Yes
9 17 kg	Hypothermic Renal function	14 normo 37 cooling 8 static 31 warming	90	87 mgs.%	9.2	No	Yes
10 20 kg	Hypothermic Renal function	10 normo 62 cooling 20 static 44 warming	124	-	11.7	Sacrificed	Yes

FIGURE III, 18.

Results of the dogs in which renal
function studies were performed.

(2) Methods:

(a) Operative and Bypass Procedure:

The 10 dogs were divided into two groups. In 8 of them profound hypothermia was induced, as has already been described (Section C). As a control, the other 2 dogs were subjected to "high flow" normothermic complete bypass. The only differences in the procedure for these 2 dogs were that a right thoracotomy approach was used; that both venae cavae were cannulated through the right atrial appendage; that the bypass was complete from the beginning; and that the dogs were not cooled.

The additional procedures performed in the 10 dogs were as follows. A needle was inserted into a vein in one of the forelimbs and a second into a vein in the right hindlimb, for intravenous infusions during the experiments. One or both ureters were cannulated to obtain urine specimens. The ureters were exposed through a small flank incision and dissected out retroperitoneally. The tip of a polyethylene catheter was inserted via the ureter into the renal pelvis and tied firmly in place.

As in all the dogs in this chapter, the rectal and mid-oesophageal temperatures were noted, as were the blood pressure variations.

(b) Renal Function Investigations:

Renal function studies were undertaken in only 9 of the 10 dogs. The remaining dog was not investigated because of faulty ureteric catheterisation which resulted in blood-stained urine.

In the hypothermic experiments the bypass was divided into four stages:

1. a period of bypass without active cooling, varying from a few minutes to half an hour,

2. this /...

2. this was followed by a period of cooling to about 10 degrees centigrade, often in stages,
3. then came a static period without active cooling or warming, followed by
4. a period of active rewarming.

The urine collections were obtained from the polyethylene catheter which had been tied in one or both ureters. The collections were obtained over accurately timed intervals. They were begun at least 20 minutes after the intravenous infusions had been begun, and from 7 to 60 minutes before bypass was commenced, to enable pre-bypass control estimations to be made. After the completion of the bypass, urinary function was followed in 8 of the dogs for a further 10 to 79 minutes, so that post-bypass estimations could be performed.

Blood samples were taken every 10 to 15 minutes throughout each experiment, usually at the mid-point of each urine collection period.

Each dog received two intravenous infusions throughout the experiment. The one, which was given into the forelimb, consisted of a 10 percent solution of dextrose in water, and this was run at a rate to ensure a urinary flow of 1 to 6 ml. per minute, prior to bypass. No attempt was made to stabilise the urinary flow. The other infusion, which was given through the needle in the vein in the right hindleg, consisted in each case of 1.5 G. creatinine, dissolved in a litre of 0.9 normal saline. This was run at about 4 mls. per minute via a constant rate drip apparatus. Each dog received a priming dose of 0.5 G. creatinine.

Twenty minutes were allowed for equilibration before the urine or blood collections were made.

In addition, 2.4 G. of PAH was included in this second drip, and a priming dose of 1.8 G. PAH was administered. For certain technical reasons, including the high dosage used, the PAH estimations were, to some extent, inaccurate, and have therefore been omitted from the discussion.

With the institution of bypass, the serum creatinine level was immediately lowered as the dog's creatinised blood was diluted with the fresh donor blood used to prime the bypass machine. Conversely, as hypothermia proceeded and the urinary excretion of creatinine diminished, the serum level tended to rise. Thus the constant infusion of creatinine was not, in itself, sufficient to ensure a constant serum level. For this reason, blood samples were taken every 10 to 15 minutes for the estimation of serum creatinine.

Each urine and blood sample was analysed for osmolality, creatinine, sodium and potassium, and each urine sample for protein content. Urine volumes were measured to the nearest 0.1 ml. Osmolality was determined by a Fiske Osmometer, accurate to 2 percent. Creatinine and quantitative urinary protein were measured following the methods described by King and Wootton (King and Wootton, 1956). Sodium and potassium concentrations were determined by flame photometry. The glomerular filtration rate was equated with the creatinine clearances, which were calculated for the periods during which each urine sample was collected. Where the appropriate blood sample had

not /,...

not been taken at the midpoint of the urine collection period, the serum creatinine level for this point has been calculated by simple proportion. The percentage of filtered sodium excreted was calculated

$$\frac{U_{Na} V}{P_{Na} C_{cr}} \times 100$$

and the percentage of filtered water excreted was calculated

$$\frac{U V}{C_{cr}} \times 100$$

(3) Results:

Figure III, 18, presents a general outline of the experiments. The Figures III, 19 to 22, present the results with regard to renal function in graphic form.

(a) Normothermic Perfusion Results:

The results obtained in the two normothermic control dogs were identical. Figure III, 19, depicts the events occurring in dog No. 8. It can be seen that, with the institution of normothermic bypass, a continuation or exaggeration of pre-bypass trends occurred. The urinary osmolality and the potassium concentration continued to rise, and the creatinine clearance and urine volume continued to fall. The exception to this continuation of pre-bypass trends was the fall which was observed in the urine sodium concentration. Calculation shows that in this dog the percentage of filtered water excreted fell from about 13 percent to 7 percent as a result of bypass.

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DOG 8. NORMOTHERMIC RENAL FUNCTION.

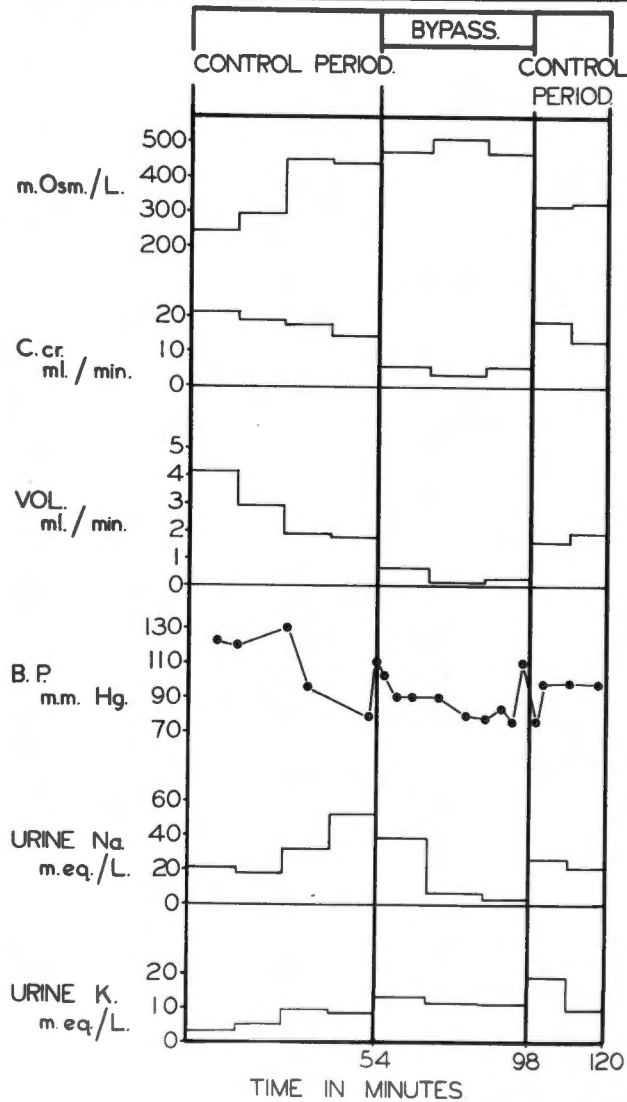


FIGURE III, 19.

A graph of the results obtained in Renal Dog No. 8 during a normothermic perfusion.

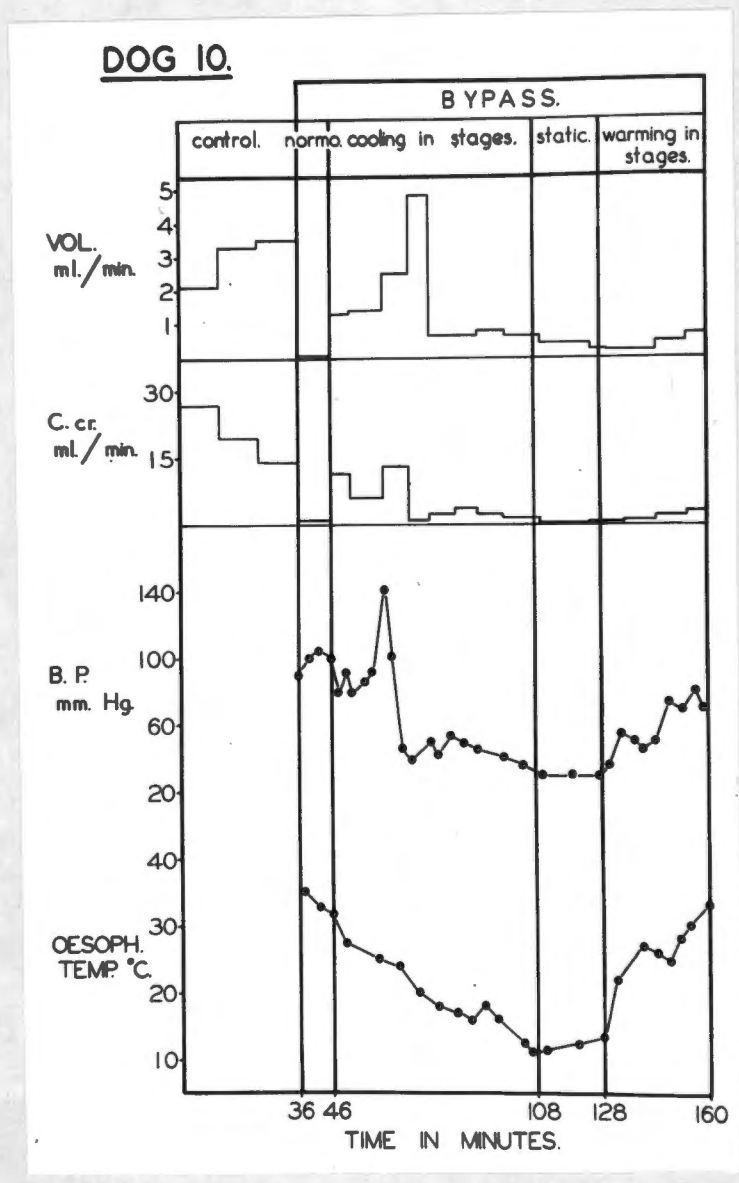


FIGURE III, 20.

A graph depicting some of the results obtained in renal Dog No. 10, during a hypothermic perfusion.

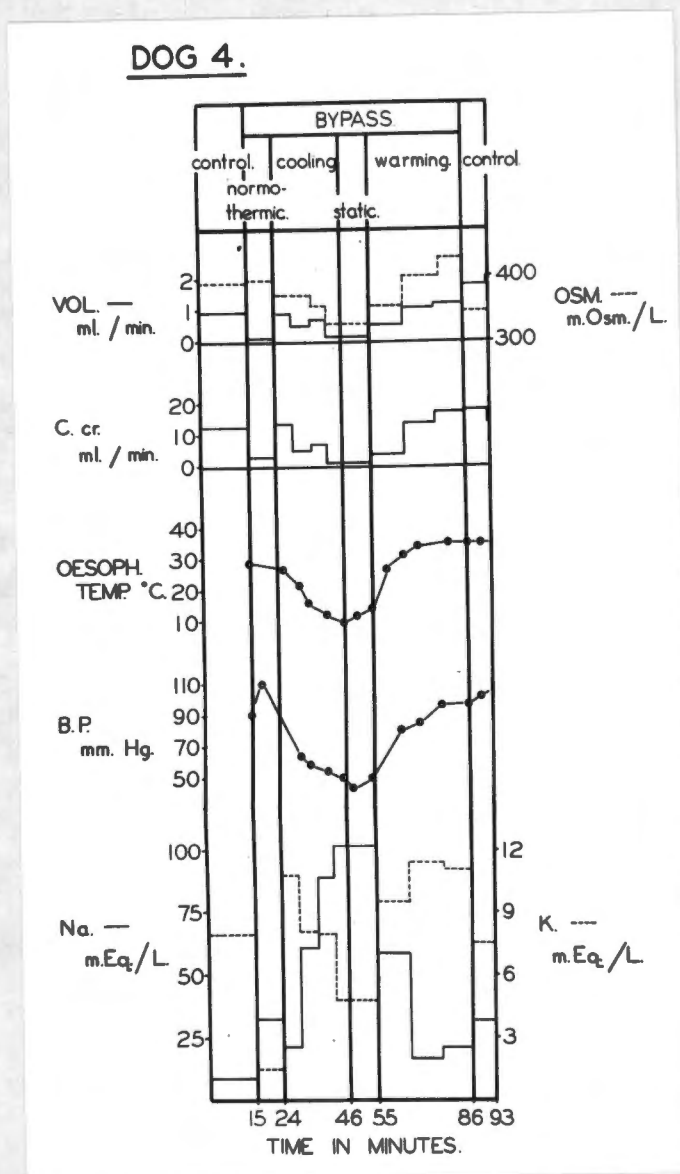


FIGURE III, 21

A graph depicting the results obtained from renal function studies on Dog No. 4, during hypothermic perfusion.

PROTEINURIA IN HYPOTHERMIC DOGS.

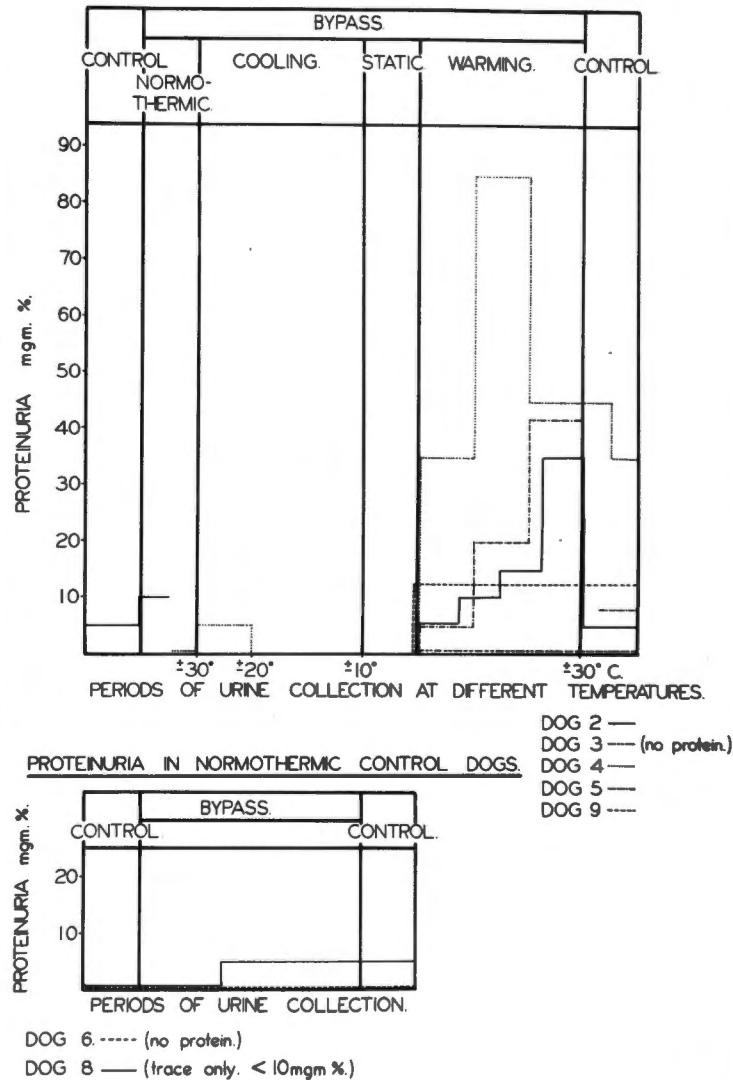


FIGURE III, 22.

These graphs show proteinuria occurring in dogs on which renal function studies were performed. The top graph shows the results of these experiments using hypothermic perfusion and the lower graph shows those using normothermic perfusion.

The percentage of filtered sodium excreted similarly fell from approximately 5 percent to 0.2 percent during bypass, to rise again to approximately 2.2 percent immediately afterwards.

After the completion of the bypass, a sharp rise occurred in creatinine clearance, in urine volume and in urinary sodium concentration. The osmolality of the urine diminished.

(b) Hypothermic Perfusion Results:

Dog No. 4 (Figure III, 21) was selected for discussion, as the findings were representative of the whole group of hypothermic dogs. The findings in this dog were as follows:

(1) Creatinine clearance, urine volume and blood pressure:

With the institution of bypass, prior to cooling, a fall occurred in the urine volume and creatinine clearance, as in the normothermic dogs, despite the fact that the blood pressure was relatively well maintained at this stage.

Immediately active cooling was instituted, over the course of the first three collection periods, there was a marked rise in the creatinine clearance and urine volume. This took place despite a fall in blood pressure.

As cooling and bypass continued, the blood pressure fell progressively, in spite of

a constant flow perfusion rate, and with this a concomitant fall in the creatinine clearance and urine volume occurred.

The above changes were reversed on rewarming.

On discontinuing the bypass, after rewarming, no drop occurred with the creatinine clearance. At this stage the urine volume increased to levels exceeding the initial control volume.

(11) Urinary sodium and potassium, and the percentage of filtered water excreted:

With the commencement of active cooling on bypass, the sodium level in the urine rose to approach the serum level.

Calculation shows that the percentage of filtered sodium excreted rose from approximately 1 percent to 13 percent at the coldest phase, to fall again to approximately 1 percent with active rewarming. In addition, the potassium level in the urine fell to approach serum levels.

The percentage of filtered water excreted rose from approximately 6 percent to 16 percent, and returned to approximately 6 percent on rewarming.

As occurred with the urine volume and creatinine clearance, the changes noted during cooling in the urinary sodium

and /...

and potassium concentrations were reversed with rewarming.

(iii) Urinary osmolality:

With the commencement of active cooling on bypass, the urinary osmolality fell to approach serum levels. This change was reversed with active rewarming.

Immediately after the bypass, there was a drop in urinary osmolality due to the diuresis (increased urine volume) which occurred.

(c) An Additional Finding in dog No. 10:

The results obtained in dog No. 10, as in the other hypothermic dogs, were similar to those shown in Figure III, 21, for dog No. 4. In addition, as can be seen in Figure III, 20, 14 minutes after the commencement of active cooling, a transient abrupt rise in arterial pressure was brought about as a result of an accidental increase in the perfusion flow rate. This was immediately reflected by a marked rise in both urine volume and glomerular filtration rate (creatinine clearance).

Calculation in this dog reveals that the percentage of filtered water excreted rose from approximately 23 percent to 72 percent when the dog was rendered profoundly hypothermic.

(d) Proteinuria:

An estimation of proteinuria was made in all the dogs, except dog No. 10. The concentration of urinary protein during these experiments can be seen in Figure III, 22.

In the hypothermic dogs at 10 degrees centigrade, the urine was protein-free, but immediately on commencement of rewarming, protein appeared. This reached levels of between 10 and 90 mgs. percent. Only one of the hypothermic dogs tested failed to develop a proteinuria (dog No. 3). For the sake of simplicity, dog No. 1, in which the circulation was stopped during the hypothermic phase, and which also developed proteinuria, was not included in Figure III, 22.

This marked proteinuria did not occur in the 2 normothermic control dogs. In fact, no protein was present in the one dog's urine and only a trace of protein was present in the other.

(4) Discussion:

Normothermic control dogs were included to demonstrate that the additional changes which occurred, with the addition of profound hypothermia to cardiopulmonary bypass, were due to the profound hypothermia per se, and not to some difference in the bypass technique. The effect on renal function of a normothermic bypass, both with "high" and with "low" flow rates, has been studied in the past (Andersen, 1958; Beall, Cooley, Morris and Moyer, 1959; Morris, Awe, Bender, Cooley and DeBakey, 1958). Semming stated that, even with "high" flow rates, effective renal plasma flow and glomerular filtration rate were significantly depressed (Semming, Andres, Bornstein, Herberg and Andersen, 1960). Anaesthesia alone has been shown to cause a depression in renal function, but with light anaesthesia, as used in these experiments, this may not be at all marked (Fapper, 1953).

To contrast the events which took place during bypass only, with those which occurred during bypass associated with hypothermia, a period of bypass without active cooling was undertaken in most of the dogs, prior to the induction of hypothermia. By this stage, in some of the dogs, there had however been some fall of body temperature.

A grossly diminished glomerular filtration rate, in the presence of active renal tubular function, must lead to a rise in urinary osmolality and a fall in the percentage excretion of filtered water and sodium. This, in fact, was seen in the normothermic control dogs, and in the control bypass period before active cooling in the hypothermic dogs (Figures III, 19 to 21). This was a constant finding in all the dogs where it was studied. Thus the changes which occurred during this period may readily be accounted for by the drop in glomerular filtration rate which was observed in the presence of unimpaired tubular function, and there is no need to look for a more complex explanation.

The marked drop in glomerular filtration rate which occurred in the presence of a relatively well maintained blood pressure was consistent with the finding of Corday, that one of the earliest mechanisms utilised to maintain systemic pressure is renal vasoconstriction (Corday and Williams, 1960).

These findings contrasted sharply with those observed when profound hypothermia was added to the cardiopulmonary bypass (see Figures III, 20 and 21).

The percentage of excreted sodium and water in the urine increased progressively with cooling. This indicated increasing failure of tubular re-absorption, and was reflected in the decline of urinary osmolality towards serum levels. A fall in the urinary

potassium /....

potassium similarly reflected failing active tubular transport. The pattern of events was similar throughout this series. It was noteworthy that as much as 72 percent of the filtered water was excreted as urine in dog No. 10 (Figure III, 20) when it had been rendered profoundly hypothermic.

Figures III, 20 and 21 indicate the progressive drop in blood pressure which took place with cooling, despite the constant "high" flow perfusion rate. This was an invariable finding and was felt to be, at least in part, due to the impairment of the autonomic nervous system function which occurred with cooling and which was accompanied by a shift of blood from the bypass apparatus into the dog (see Section 9). Even during the normothermic perfusion, the blood pressure was lowered (but not progressively so) despite the "high" flow perfusion rate (Figure III, 19). This, too, was felt to be due to an altered autonomic response in the form of peripheral vasodilatation (Senger, Robicsek, Taylor, Rees and Stam, 1960).

With the institution of active cooling, the glomerular filtration rate and the urine volume rose promptly, despite a concomitant fall in blood pressure (see Figures III, 20 and 21). The phenomenon was present in all the dogs. Segar, (Segar, Riley and Berila, 1956; Segar, 1958), and others, have shown that hypothermia induces a marked diuresis in the dog. The finding of a diuresis immediately on cooling confirmed this, and also revealed that at least two mechanisms were at play. One was the transient increase in glomerular filtration rate, which led to an immediate and marked increase in urine volume; the other mechanism was the progressive failure of tubular re-absorption of water, which resulted in a diuresis during

profound /...

profound hypothermia, out of normothermic proportion to the greatly reduced glomerular filtration rate. The importance of the latter mechanism in hypothermic diuresis has not hitherto been generally appreciated.

A more obvious relationship between glomerular filtration rate, urine volume and blood pressure than appeared during the normothermic bypass was present during active cooling and rewarming, as evidence by:

- (1) the fall and rise which occurred in the glomerular filtration rate and urine volume, associated with the fall and rise in blood pressure (Figures III, 20 and 21),
- (2) the accidental increase in perfusion rate which occurred in dog No. 10, causing a transitory rise in blood pressure, which was associated with an immediate rise in glomerular filtration rate and urine volume (Figure III, 20).

A most important and significant finding in this study was the immediate reversal, on rewarming, of the changes brought about by profound hypothermia.

In the light of this, if the degree of re-absorption of filtered water, sodium and potassium, and the elaboration of concentrated or dilute urine, were used as indices of tubular function, it is evident that tubular function returned promptly to control levels on rewarming. In only one of the 6 hypothermic dogs in which post-bypass function was studied did the glomerular filtration rate not return immediately to pre-bypass levels, after the termination of bypass.

Five of the 6 hypothermic dogs in which the urine was tested for protein developed proteinuria on rewarming. If proteinuria per se is an indication of renal damage, it must be concluded that hypothermia /...

hypothermia, or the rapid rewarming of the cold organ, can damage the canine kidney in the presence of a "high" flow perfusion rate. It is the author's opinion, however, that proteinuria per se is not necessarily an indication of renal damage (cf. in athletes).

It thus appears that the use of the technique of profound hypothermia, which is proving such a useful aid in certain branches of modern surgery, is justified, as the extreme changes in renal function which take place during its application are promptly reversed on rewarming.

The effect of cold on the kidney in both dog and in man, in the conditions usually induced by surface cooling, has been extensively studied (Andersen and Nielsen, 1955; Bergstrand and Sterky, 1954; Blatteis and Horvath, 1958; Hong, 1957; Hong and Boylan, 1959; Kanter, 1959; Miles and Churchill-Davidson, 1955; Morales, Carbery, Morello and Morales, 1957; Moyer, Morris and DeBakey, 1957; Moyer, 1959; Page, 1955). Even at these temperature levels Segar was able to detect some disturbance of renal tubular function (Segar, Riley and Barila, 1956; Segar, 1958).

One of the most interesting aspects of this study was the effect of profound hypothermia on the tubular transport mechanisms of the kidney. Further work on this aspect, which is being done at present, is beyond the scope of this thesis. It is sufficient to point out here that the changes which occurred in the urinary constituent concentrations with the progression of cooling indicate that the specific enzyme systems responsible for the re-absorption and secretion of these substances in the kidney tubules, were being blocked by the cold.

(5) Conclusions:

In this section, the results were discussed of the 7 dogs which were used to study the variations in renal function that occurred during and immediately after profound hypothermia in association with the bubble oxygenator system, and of the 2 dogs used to study the variations that occurred during "full flow" normothermic complete bypass. In concluding, the relevant important factors which have been brought to light during these experiments will be listed.

(a) The changes in renal function which occur during bypass, without hypothermia, are those associated with a fall in glomerular filtration rate in the presence of normally functioning renal tubules. This fall in glomerular filtration rate is apparently out of all proportion to the relatively well maintained blood pressure. Subsequent to bypass, when the glomerular filtration rate returns to control values, these changes are reversed.

(b) The changes in renal function which occur during bypass with profound hypothermia, contrast sharply with the above.

- (i) Tubular function (as evidenced by the changes in the urinary osmolality, the urine sodium and potassium concentrations, and the increase of excretion of filtered water and sodium), becomes progressively paralysed.
- (ii) A progressive drop in blood pressure occurs despite the maintenance of a constant "high flow" rate perfusion.
- (iii) Initiation of hypothermia induces a transitory increase in glomerular filtration rate and urine volume.

(iv) /...

(iv) A more obvious relationship between glomerular filtration rate, urine volume and blood pressure occurs.

(e) Rewarming after profound hypothermia leads to a prompt reversal of the above changes.

(d) This reversal is maintained in the immediate post-bypass period.

(e) During the induction and maintenance of profound hypothermia, there is no proteinuria. With rearming, proteinuria immediately occurs. The significance of this is not yet certain.

(f) In the author's opinion, the use of the technique of profound hypothermia, which is proving so valuable an aid in various branches of surgery today, has been justified as, despite the extreme changes in renal function that occur during its application, these are reversed promptly on rearming.

SECTION G - METABOLIC STUDIES DURING AND AFTER THE PROFOUND HYPOTHERMIA EXPERIMENTS.

Ever since Claude Bernard emphasised that, in spite of the wide range of variation that occurs in the composition of the external environment of man, the "milieu interieur" by contrast is kept remarkably constant by the intervention of many compensatory mechanisms, scientists have realised the importance of maintaining this constant state. "If the stresses imposed on the system become too great, the composition of the internal environment may alter significantly, often with disastrous effects Living cells are always undergoing change, but to

survive /....

survive and function normally, their integrity in all respects, i.e. their form, chemical composition and chemical organisation, must be constantly and fully restored and preserved" (Wright, 1952).

The induction of profound hypothermia, by deliberately reducing the body temperature in dog and in man, represents just such a great stress, which must alter the composition of the internal environment. Thus the occurrence of variations in parameters studied during such a procedure is not surprising.

With the tremendous advances in science in recent years, the understanding of normal physiology has increased beyond the widest dreams of men like Claude Bernard. Nevertheless, by reducing body temperature, man is creating a completely new field of unknown physiology in which a different internal environment exists. This internal environment will have to be investigated anew before its implications can be fully comprehended.

It has already been shown that dogs tolerate profound hypothermia well for short periods, with a return to apparent normality on rewarming, and that, although their renal function varies, this also returns to normal. This safety will also be shown to apply to man, in a later Section, and the technique will be demonstrated to be a useful aid in performing cardiac surgery. These facts in themselves are insufficient. When man applies such a technique to other human beings, he must strive to attain a full knowledge of the implications of what he is doing. An understanding of the physiology of profound hypothermia, however, can only be attained by achieving full co-operation between workers in many branches of science and medicine throughout the world.

During /...

METABOLIC DOG NO.	TOTAL DURATION OF BYPASS.	LOWEST OESOPH. TEMP. IN °C.	LOWEST ART. PRESSURE DURING COLD PHASE	BLOOD INTO DOG WHEN COLD.	AMOUNT OF NaHCO ₃ GIVEN.	FINAL PLASMA HAEMOGLOBIN.
1	60 minutes	10.0	50 mm.Hg.	300 cc.	30 cc.	78 mgs.%
2	49 minutes plus 26 mins.off	11.0	-	-	50 cc.	-
3	60 minutes	9.2	68 mm.Hg.	-	40 cc.	100 mgs.%
4	66 minutes	10.9	75 mm.Hg.	300 cc.	40 cc.	176 mgs.%
5	62 minutes	9.8	60 mm.Hg.	200 cc.	40 cc.	47.2 mgs.%
6	65 minutes	10.0	110 mm.Hg.	400 cc.	Nil	85 mgs.%
7	61 minutes	13.8	70 mm.Hg.	500 cc.	Nil	76 mgs.%
8	56 minutes plus 17 minutes	10.0	60 mm.Hg.	850 - 900 cc.	Nil	317 mgs.%

FIGURE III, 23.

Results of the metabolic studies on dogs.

During these experiments, the "milieu interieur" of the dogs changed. A study of a few parameters was undertaken to determine what changes would occur with a view to increasing the knowledge of this new technique, and thereby ultimately increasing the safety of its application in man.

In this Section, 7 of the 8 dogs in which the variations that occurred in the venous pressure, the arterial pressure, the blood balance, the blood oxygen and carbon dioxide concentrations, the electrolyte pattern and the pH's, were studied, will be discussed. In addition, the blood destruction that took place during the procedures will again be mentioned.

(1) Material:

Eight dogs (Figure III, 23) in the series of 19 subjected to profound hypothermia (Figure III, 4) are included in this section. As a technical hitch occurred with the bypass during the perfusion in the second dog (the ninth of the general series) necessitating the switching off of the bypass apparatus, the collection of samples in this dog was discontinued.

Thus, detailed investigations were undertaken in only 7 of the 8 dogs, and the study of their responses to the induction of profound hypothermia will be discussed.

(2) Methods:

A detailed description of the bypass and post-bypass periods in these dogs has been given in Section C of this Chapter.

In each of the dogs an unvaried routine procedure was adopted. Figure III, 24, shows in outline the plan followed. The operative and bypass details are shown on the left, while times at which the specimens were taken in relation to these are shown on the right.

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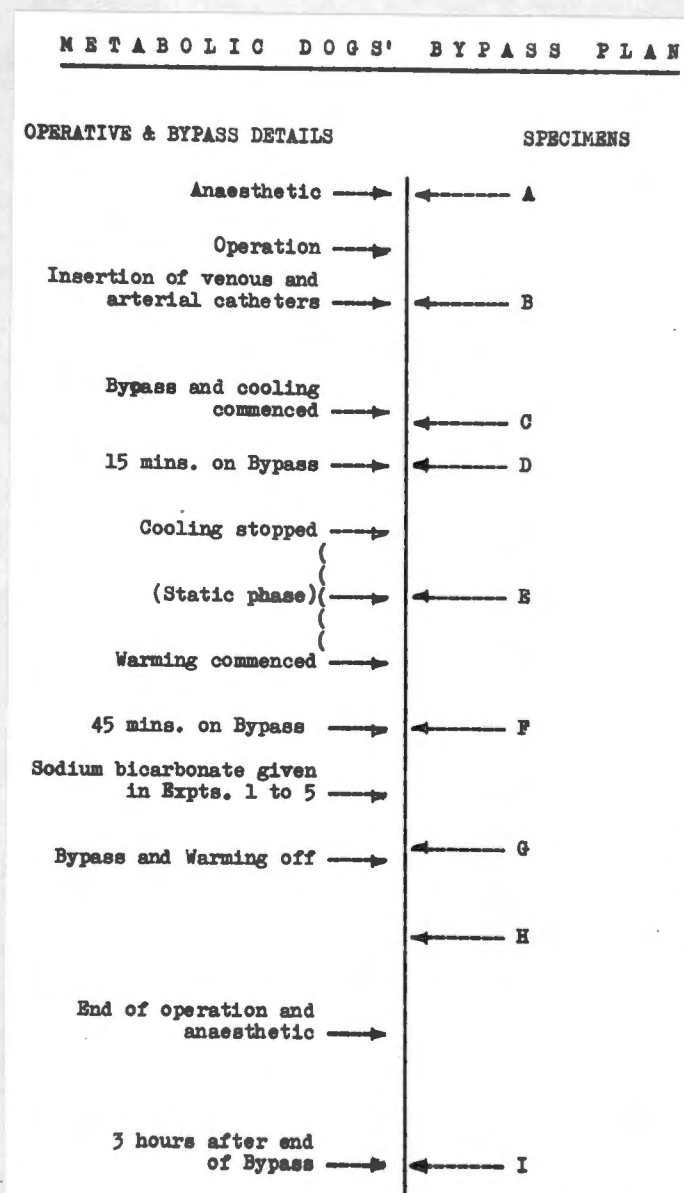


FIGURE III, 24.

A plan showing the times at which blood specimens were taken from the dogs on which metabolic studies were performed, in relation to the bypass.

This Table is self-explanatory and will not be discussed further.

The venous and arterial pressures were recorded by U-tube Manometers connected to the inferior vena cava and the femoral artery by means of polyethylene cannulae (Figure III, 10). The low-mid-oesophageal temperature was recorded using a special oesophageal temperature lead attached to the Electric Universal Thermometer (Figure III, 9).

Venous and arterial blood samples were used to test for the following: the oxygen saturation, measured using the "Brinkman Haemoreflector"^{**}, and the carbon dioxide content, measured using the method of van Slyke (Peters and van Slyke, 1932).

Arterial blood samples were used to determine the pH's, using the "Metrohm Electrodes for Blood pH"^{**}. These samples were collected in special bottles.

Venous blood samples were used to determine the following: the serum sodium and potassium levels, using the "Beckman flame photometer"^{***}, the chloride level, as described by Varley (Varley, 1954), and the plasma haemoglobin present, by the method described by Crosby (Crosby and Furth, 1956).

During each bypass, a special note was made of the blood balance of the bypass apparatus at various stages, paying particular attention to blood accumulating in the dog and not returned to the apparatus.

(3) Results and Discussion:

Figure III, 23, presents a general outline of some of the details of the experiments. Figures III, 25 to 31, show the results of the studies of various parameters in 7 of the 8 dogs. Each parameter studied will be dealt with separately.

(a) /.....

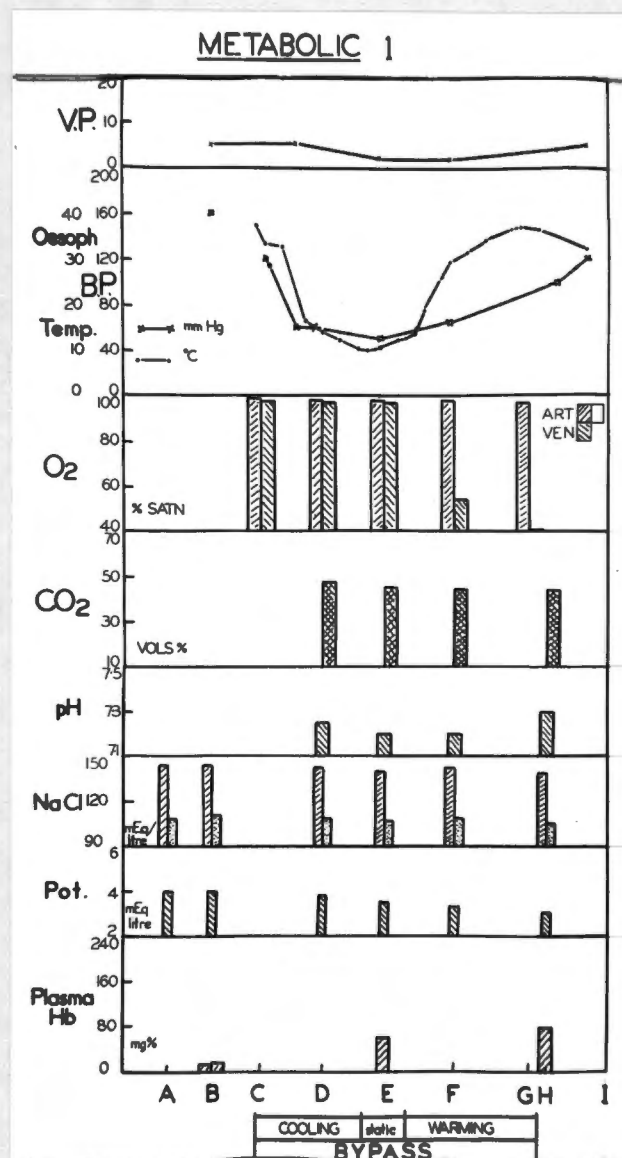


FIGURE III, 25.

A graph of the results of the metabolic studies performed on Dog No. 1.

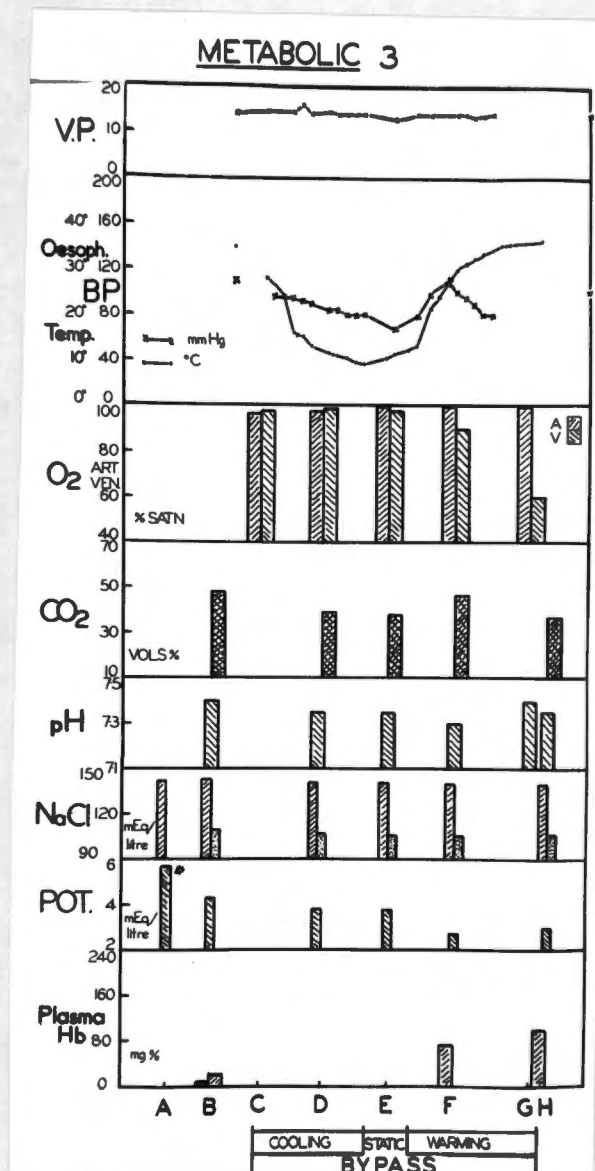


FIGURE III, 26.

A graph of the results of the metabolic studies performed on Dog No. 3.

(a) Venous pressure: In 4 of the cases almost no variation occurred in the venous pressure throughout the procedure. In 2 (dogs Nos. 4, Figure III, 27, and 8, Figure III, 31), a rise occurred at or just after going on bypass, but it was marked in only one of these. In another dog (dog No. 5, Figure III, 28), there was a drop in pressure at this same point. In these 3 dogs the pressure remained steady after this change. Thus, in all the dogs the central venous pressure remained constant throughout the remainder of the period of cooling and rewarming.

It is felt that the variations in venous pressure are not significant, and that this parameter requires no further study. It is not surprising that, on the three occasions when a change took place, it occurred at or just after going on bypass, as it was at this point that a change in the circulatory haemodynamics took place, when most of the venous return commenced to drain into the bypass apparatus, through the single catheter in the right atrium.

It is noteworthy that no change was found during the remainder of cooling and during rewarming, despite marked changes in such parameters as blood pressure and blood balance.

(b) Arterial pressure:

(i) During cooling, a drop in arterial pressure occurred in all the cases, despite the maintenance of constant and relatively "high flow" perfusion rates. Some fall had already occurred in most of the dogs prior to commencement of bypass, probably because the blood lost during the opening of the chest was not replaced promptly.

The fall that took place during cooling was usually progressive until the lower temperature ranges were reached, but the actual degree of drop was widely variable, being much more in some than in

others /.....

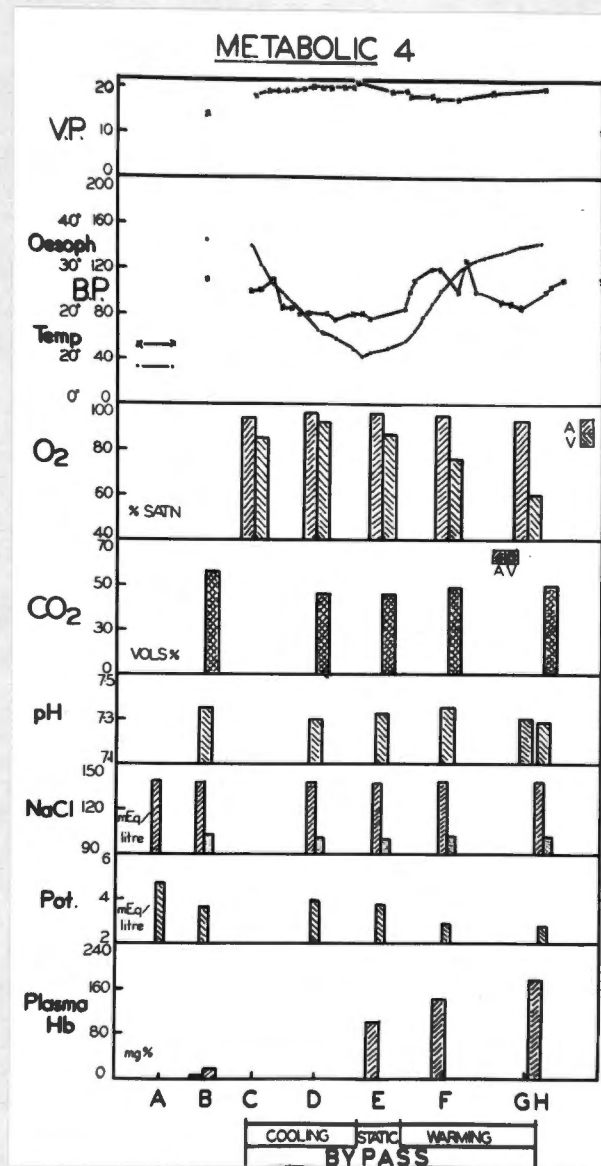


FIGURE III, 27.

A graph of the results of the metabolic studies performed on Dog No. 4.

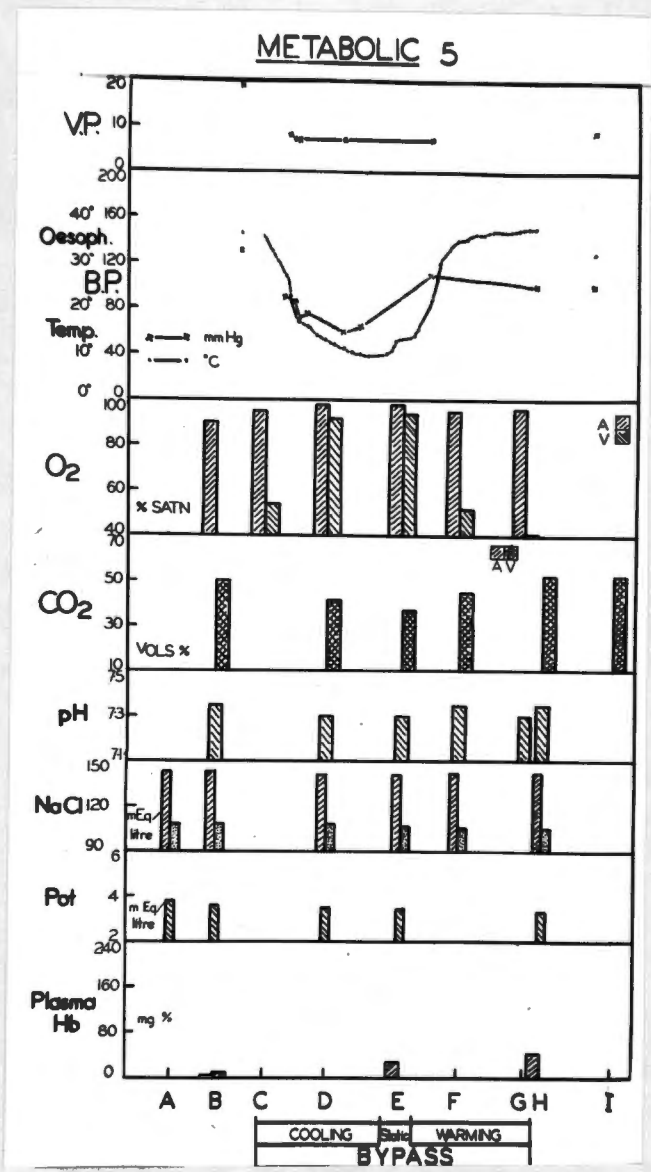


FIGURE III, 28.

A graph of the results of the metabolic studies performed on Dog No. 5.

others. It did, however, drop to below 80 mms. of mercury in all except 1 dog. In addition, this progressive drop was marked in 3 of the cases by a transient rise in pressure soon after the commencement of bypass and cooling.

It is not quite clear why this progressive drop in pressure during cooling occurred. It is known that, when a dog is put on normothermic bypass using similar flow rates, some drop in blood pressure does occur. This has been shown to be due to an altered vasomotor response (Sanger et al, 1960). During surface hypothermia the failing heart causes a drop in blood pressure (Bigelow et al, 1950, b), but in the dogs in this section, the circulation was maintained with an extracorporeal pump. Of course, the possibility exists that some unknown factor, brought about by the cold itself, causes this drop. The probable importance of the role played by the paralysis of the autonomic nervous system by the cold will be discussed later.

The drop in blood pressure which occurs so consistently during the induction of this type of hypothermia is felt to be the result of the interplay of many factors, the paralysis of the autonomic nervous system being the most important, and it does not represent a hazard as the protective action of the hypothermia on the tissues is operative. The fact that the fall in blood pressure occurs despite a constant venous pressure, is also of interest.

(11) During rewarming: In 4 of the dogs a definite rise in the arterial pressure occurred as soon as active rewarming was commenced, (dogs Nos. 1, 3, 4 and 6). In dog No. 5, a rise commenced as soon as active cooling was discontinued, but it began to fall again as warming progressed. In dog No. 7, the rise was slight and also began to fall towards the end of rewarming. In dog No. 8, the pressure remained low during rewarming and only rose at the end of the procedure. Even in 3 of the 4 dogs in

which /...

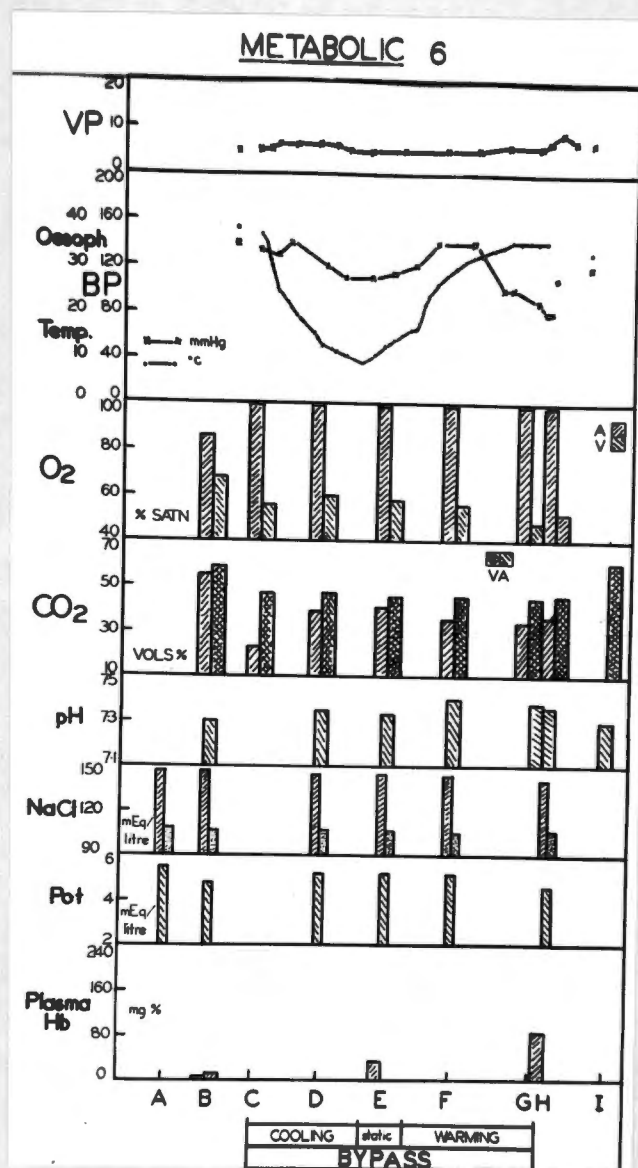


FIGURE III, 29.

A graph of the results of the metabolic studies performed on Dog No. 6.

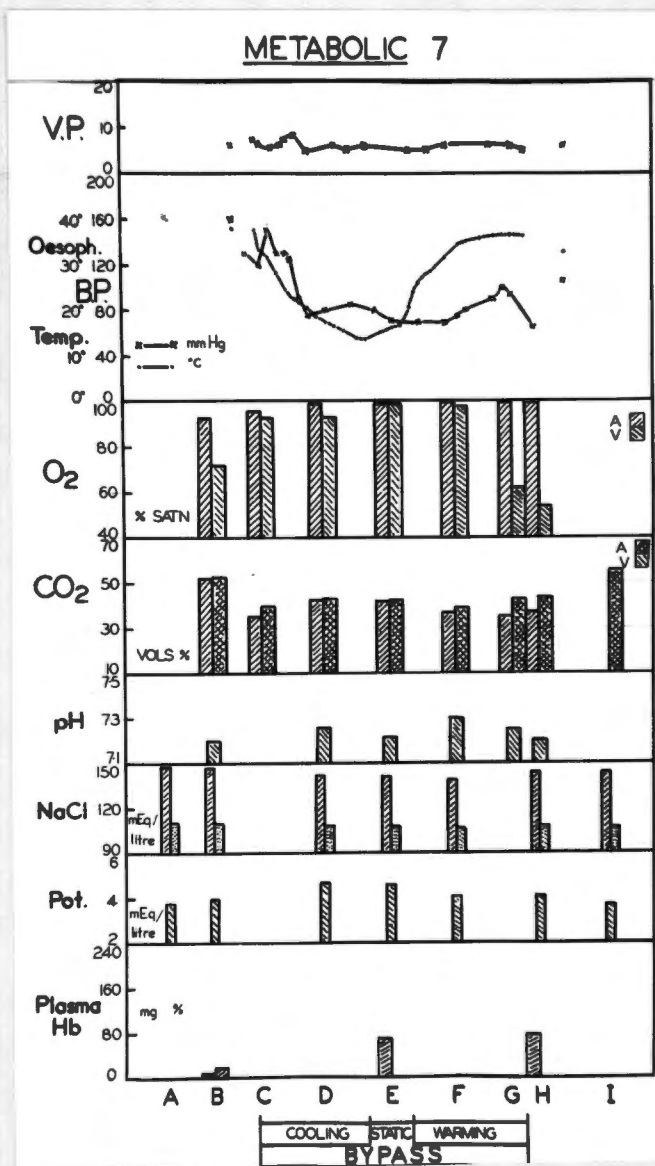


FIGURE III, 30.

A graph of the results of the metabolic studies performed on Dog No. 7.

which the pressure rose, there was a later fall just before going off bypass.

Once the bypass had been discontinued and the blood balance corrected, the arterial pressure returned to a satisfactory level in all the dogs.

The relatively low level of arterial pressure present in most of these dogs at the end of the bypass and during the phase immediately following bypass was probably the result of inadequate attention to the correction of blood balance, promptly, at this stage. (In the patients, where this is carefully watched, a low blood pressure does not occur at this stage). In fact, in many of the dogs, when the bypass was stopped, it was noticed that blood had accumulated in the apparatus at the expense of the dog. (During the hypothermic phase the reverse occurs - Figure III, 23 and (c) below.)

No matter what the cause of the low blood pressure, firstly during cooling and subsequently at the end of bypass, the significance is that this does not produce permanent impairment. The arterial pressure always returns to a satisfactory level soon after completion of the perfusion, once the blood balance has been corrected.

(c) Blood Balance: A note was made of the blood balance of the bypass apparatus during the procedure in 6 of the 8 dogs (Figure III, 23). A progressive shift of blood from the machine into the dog was noted in all cases. During the "static" phase the level of blood in the bypass machine had fallen to its lowest point, which varied in output from 200 to 900 cc. of blood. During active warming, the blood returned from the dog, however, and, as already mentioned, by the end of the perfusion excess blood was usually present in the machine.

On the /....

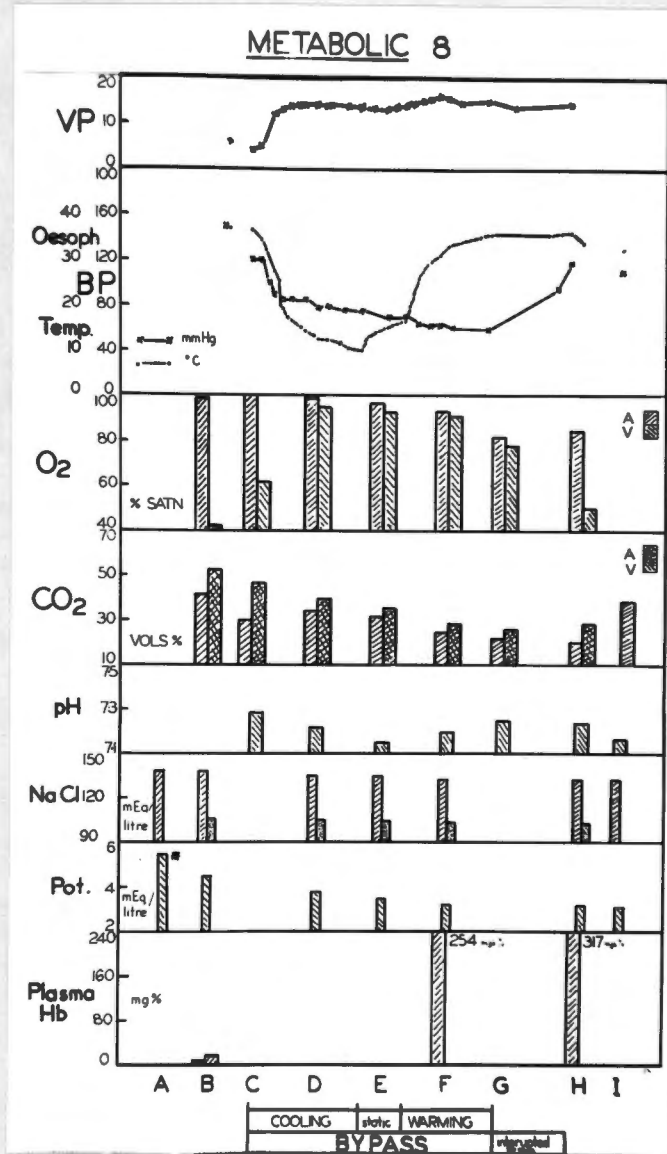


FIGURE III, 31.

A graph of the results of the metabolic studies performed on Dog No. 8.

On the one hand, the loss of blood from the apparatus did not correspond in any way to the degree of fall which occurred in the blood pressure. Thus, in dog No. 6 (Figure III, 29) where the least blood pressure fall occurred, the apparatus lost 400 cc. of blood into the dog during the cold phase, and in dog No. 5 (Figure III, 28) where the fall in pressure was fairly marked, only 200 cc. of blood was lost from the apparatus.

On the other hand, with this extra blood entering the dog, a rise in venous and arterial pressures might have been expected. This did not occur and, in fact, the arterial pressures fell while the venous pressures remained constant.

What is the cause of the shift of blood into the dog? Others have also noted this shift. Robard, in 1951, felt that it was due to changes in various vascular beds in response to neurogenic regulatory mechanisms from the central nervous system (Robard, Saiki, Malin and Young, 1951). Simpson, too, found that "during cooling there is almost invariably a loss of a small amount of blood from the machine into the animal", and he felt this to be due to the mechanism described by Robard (Simpson, Gibson and Bloomfield, 1960). Lindberg noted a diminished venous return during cooling with an extracorporeal circulation, which increased again on warming, and proposed the formation of an intravenous pool of blood as the explanation for this phenomenon (Lindberg, 1959). It has been subsequently shown that, as cooling progresses, so the autonomic nervous system is first impaired and later paralysed (Holmdahl, 1961). Thus, the most likely explanation is that during hypothermia, as a result of the autonomic nervous system paralysis, blood pools in certain areas of the body. It is probably on the basis of this alone that this shift of blood

into /.....

into the dogs occurs during cooling.

When the arterial pressure was discussed, the possibility that the paralysis of the autonomic nervous system played an important part in causing the variations that occurred in the arterial pressure, was mentioned. There is, however, no obvious correlation between the blood pressure level and the blood balance, and in addition, the blood pressure does not regularly rise as the blood balance rights itself during warming. This probably indicates that the variation in blood pressure, unlike that of the blood balance, is due to the combined effects of a number of factors.

A further point of importance that arises is that, with a prior knowledge of this loss of blood from the bypass apparatus (up to 900 cc. in one dog), the pump technician can be prepared by having sufficient donor blood available to meet a requirement of this magnitude.

(d) Venous and Arterial Blood Oxygen Saturations: The oxygen saturation of the arterial blood (the blood leaving the oxygenator) was found to be consistently high throughout all the bypasses.

The reason for this high arterial oxygen saturation is undoubtedly that the bubble oxygenator, by virtue of its method of oxygenation, is more than adequate in oxygenating the blood passing through it.

In the 4 dogs in which the pre-bypass arterial oxygen saturation was tested it was found to be normal. In 2 of the 3 dogs where pre-bypass venous samples were collected, they were found to have normal oxygen saturations as well. The excessively low venous oxygen saturation of 42 volumes per cent in dog No. 8

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(Figure III, 31) is difficult to explain other than on the basis of an experimental error in its estimation.

As already mentioned, the arterial oxygen saturation remained high during the cooling. In all the dogs (except dog No. 6, which will be dealt with separately), the venous oxygen saturation rose during the cooling and cold phases to approach arterial levels. In one of the dogs (dog No. 3, Figure III, 26) the estimated venous level was even higher than the arterial level at this stage. (This can be accounted for as falling within the accepted error of the experimental technique of estimation). The venous oxygen saturation at specimen C (immediately after going on bypass) was low in 2 of these 6 dogs by comparison with the others (62 and 54 volumes per cent respectively). In these 2 dogs the blood was probably taken before any appreciable cooling had occurred and thus the tissues still had a highly active metabolism.

This drop in oxygen requirement during hypothermia indicates decreased tissue metabolism taking place, which is the basis of the safety of induced hypothermia, and was demonstrated by Bigelow in one of his pioneer articles (Bigelow et al, 1950, c).

The venous oxygen saturations in dog No. 6 (Figure III, 29) presented a different picture from the other dogs. A large arterio-venous oxygen difference persisted throughout the whole bypass. This occurred in the presence of a high arterial oxygen tension, and despite the fact that when it was cold, a high flow of fully oxygenated blood was passing through its tissues. This

indicates /....

indicates two things. Firstly, oxygen was able to pass into the tissues from the cold blood in large quantities, and secondly, despite the low mid-oesophageal temperature attained in this dog (10.0 degrees centigrade), the tissues utilised a large amount of oxygen. It has been shown that the temperature of the main mass of the body tissue lags well behind that of the vital organs and the oesophagus. It is possible that metabolism took place in the warmer tissues in this dog, but why this should occur in this particular dog is not clear. On the other hand, there is no proof that the high oxygen demand was not due to active metabolism taking place in vital organs.

Whatever the reason for this dog using oxygen, the fact that one dog in this small series did require oxygen, despite profound hypothermia, is significant. The dog needed oxygen when it was cold and thus switching off the circulation completely would have been dangerous. The need for at least low flow rates whenever possible is well demonstrated.

During the rewarming and immediately after the bypass in each of these dogs, the arterio-venous oxygen difference increased, as evidenced by the fall in venous oxygen saturation. This indicates that there was an increased demand for oxygen in the tissues in these dogs, with active metabolism taking place.

If the autonomic nervous system paralysis which occurred causes intravascular pooling of blood, then it is possible that during the hypothermic phase the oxygenated blood bypasses some of these areas. With rewarming and the reversal of the autonomic paralysis, the oxygen debt that would be present in the tissues where pooling had occurred would account for the high oxygen requirement of the body during rewarming.

These/.....

These studies of oxygen saturation during hypothermia indicate that, during the actual hypothermic phase, with exceptions, there is very little demand for oxygen by the body. Thus, in most cases, switching off the circulation completely seems to be justified. Unfortunately, as the case in which oxygen requirement is going to be present during hypothermia cannot be predicted, it is obviously preferable to continue to perfuse the patient with oxygenated blood throughout the hypothermic period, even if only at "low flow" rates. These flows will serve two functions: firstly, they will cover the eventuality of a large oxygen requirement being present during hypothermia, and secondly, they will make oxygen available to meet the small metabolic requirement usually present.

During rewarming, there is undoubtedly a fairly high oxygen requirement in all cases. This is felt to be an indication for higher flow rates during rewarming, particularly at the end of this phase, than are generally utilised.

(c) Venous and Arterial Blood Carbon Dioxide Saturations:

Arterial carbon dioxide estimations were only performed in the last 3 dogs in this series.

It is a well-known and accepted fact that the bubble oxygenator eliminates carbon dioxide efficiently. The fairly high venous carbon dioxide content that was present in the blood of these dogs throughout the bypasses, thus indicates that carbon dioxide was being produced in the body. It can be inferred from this that tissue metabolism was occurring, even in the lower temperature ranges. In the last 3 experiments, arterio-venous carbon dioxide differences were present, even during the cooling and cold phases,

with /....

with the venous carbon dioxide saturation being significantly higher than the arterial in 2 of the dogs. This confirms that metabolism takes place during warming, and is an even stronger indication of metabolism occurring during the cooling and cold phases in at least some dogs, than the oxygen saturation studies.

During the actual bypass, both the arterial and venous carbon dioxide saturations were lower than before or after, with the lowest point occurring at the coldest phase. This probably is due to two factors. Firstly, the efficient elimination of carbon dioxide by the oxygenator, and secondly, the lowest metabolism occurring at the coldest phase.

This study of the carbon dioxide content of the blood during profound hypothermia, further confirms the opinion of the necessity for maintaining a flow of oxygenated blood throughout the hypothermic phase of such a cardiopulmonary bypass.

(f) pH Variations in the Arterial Blood: If blood is taken under anaerobic conditions, and cooled in the same container, when the pH is read at a lower temperature it is more alkaline in the relationship $pH_{38} = pH_t - 0.0147 (38-t)$ (Rosenthal, 1948). The reason for this change is that the blood re-equilibrates. Such re-equilibration does not occur inside the cooled animal, and Edmark, who advocates "continuous pH measurement during the course of hypothermia", states that an animal will have the same pH at 27 degrees or 18 degrees centigrade as at 37 degrees centigrade, "if the carbon dioxide pressure is held the same and metabolic acidosis or alkalosis has not developed" (Edmark, 1959).

There /....

There is no uniformity in the literature on profound hypothermia on the question of the pH changes that occur, and how they should be recorded - some are recorded at the temperature of the blood at the time of sampling, and others are recorded at room temperature or at 38 degrees centigrade. When the pH is recorded at 38 degrees centigrade, it is also not clear whether this should be expressed as such, or be corrected to the temperature of the blood at the time of sampling, using the above formula. Kenyon feels that the value of pH's at low temperatures is debatable (Kenyon et al, 1959).

Until this matter is clarified, it is difficult to draw conclusions on the results of pH estimations during profound hypothermia. In these dogs, the pH specimens were collected at various temperatures, warmed to 38 degrees centigrade in their closed containers, and read at that temperature. In the graphs these pH's show a slight fall to become more acid during the perfusion in most of the dogs. When, however, they were corrected to the temperatures of the blood when samples were taken, using the above formula, the values became alkaline during the bypass, with a reversal afterwards, in every dog.

The final pH at the end of the procedure, and afterwards, constitutes a different matter. Here the dog was again warm and the normal factors causing a change in pH were again at play. The dogs, with the exception of the last 3, were given a small amount of 4 percent sodium bicarbonate between specimens F and G (see Figure III, 24), and in these the final pH was 7.3 or higher, except in dog No. 4 (Figure III, 27) where it was 7.29. This indicates that, despite any variations that occur during the hypothermia, the dogs are normal in this respect at the end of the procedure. In the last 3 dogs, no sodium bicarbonate was administered and the pH fell as low as 7.17 and 7.20 in 2 dogs while in the third it was 7.30.

Thus /....

Thus a small shift to the acid occurred as a result of the procedure, but, as is indicated by the earlier experiments, this is readily corrected by the addition of a small amount of sodium bicarbonate.

Metabolic acidosis, as reflected by a fall in pH at the end of the procedure, does occur in "full flow" normothermic bypass, and here it is felt to be due to an inadequate perfusion, despite a "high flow" rate (Kolff, Effler and Groves, 1960). In the dogs subjected to hypothermia, the slight drop in pH that occurs when sodium bicarbonate is not administered may also be due to inadequate perfusion, occurring despite "high flows" as rewarming takes place. On the other hand, if there was pooling of blood with stagnation in some areas (due to paralysis of the autonomic nervous system) the anaerobic metabolism, however small, that would occur would possibly account for this.

These studies have led to the belief that the administration of a small amount of sodium bicarbonate during such a procedure is desirable, if not essential.

(g) Variations in the Sodium, Chloride and Potassium Levels in the Venous Blood:

The level of sodium in the plasma remained constant before, during and after the procedure. No change was expected, as no change occurs in this parameter during normothermic bypass (Callaghan et al, 1958), and during surface hypothermia alone (Reed and Gavrilescu, 1958).

Similarly, no change was found in the chloride level before, during or after the procedure.

As no change occurred in either of these parameters, it is felt that further study of the metabolism of sodium and chloride during hypothermia of this nature becomes unnecessary.

In /....

In all these experiments, except one, there was a tendency for a small but progressive drop in the potassium level during the procedure. In dog No. 7 there was an initial rise followed by a subsequent fall. This drop occurred despite a progressive increase in the number of haemolysed red blood cells present, as evidenced by the rise in plasma haemoglobin. In 2 of the experiments the initial control specimen (marked with an asterisk) was found to have haemolysis present, and this must have been due to the technique of collection. The initial level in these 2 dogs was therefore higher than normal.

A fall in the potassium level in the plasma also occurs in patients subjected to profound hypothermia with cardiopulmonary bypass, but this fall is more marked and is found to be associated with a rise in glucose levels (see Chapter Four). A similar change occurs during normothermic bypass (DeWall et al, 1957, b).

The reason for this fall is not clear, but it must be due to potassium shifting from the plasma into the cells during bypass without actual potassium loss from the body, as it subsequently corrects itself, without the administration of potassium. An increase in heart muscle cell potassium has been demonstrated during surface hypothermia (Spurr and Barlow, 1959; Beavers and Rogers, 1959, b). Further investigation in this field is necessary before its true significance will become clear.

(h) Plasma Haemoglobin Levels: An abnormal rise in plasma haemoglobin levels occurred in all these dogs during the course of the bypass. From the graphs it can be seen that the rise progressed as long as bypass was continued, but the extent of the rise varied from dog to dog. In addition, the low level present in the donor

blood /....

blood sample (the right-hand block of specimen B in the graphs), taken with the first specimen, indicated that the subsequent high levels were not due to excessive haemolysis present in the donor blood.

The progressive nature of the increase led to the belief that the cause of the rise was to be found in the bypass apparatus. In the past, using the same apparatus in dogs but without an artificial oxygenator, low levels of haemolysis were shown (Terblanche and Barnard, 1960). Thus the relatively high haemolysis present in these dogs must be due to the bubble oxygenator itself, and not to the pumps or the profound hypothermia. In clinical cases, where the bubble oxygenator was used for normothermic cardiopulmonary bypass by Dr. C.N. Barnard in Cape Town, he found that the haemolysis varied fairly constantly with the length of the perfusion, the final level usually being in the vicinity of 1 mg. of plasma haemoglobin for every minute of bypass (personal communication).

This points to the bubble oxygenator as the cause of excess destruction of blood, and may be a small point in favour of the use of another oxygenator in preference when inducing profound hypothermia.

(4) Conclusions:

In this Section, the results of studies on 7 of the 8 dogs used to observe the variations in certain parameters which occurred during and just after profound hypothermia in association with the bubble oxygenator system, were discussed. In concluding, the relevant important factors which have been brought to light during these experiments will be pointed out below.

- (a) Cooling causes a progressive drop in blood pressure: probably due to the interplay of many factors. The

most /....

most important factor is probably an altered autonomic response. It is not hazardous as the tissues are protected by hypothermia. The drop occurs in the presence of a constant venous pressure and does not correspond to the blood balance. In addition, it occurs despite a constant "high flow" perfusion rate. The factors causing blood pressure changes during these perfusions are not important in the long run, as satisfactory levels are soon attained after the bypass.

- (b) During the bypass, there is a disturbance in the blood balance when blood leaves the machine to enter the dog, despite a concurrent drop in blood pressure and normal venous pressure. The possibility is discussed of this being caused by blood pooling in the dog, due to paralysis of the autonomic nervous system by the cold. In addition, with the knowledge of the possibility of this disturbance, one can be forewarned and fore-armed with sufficient donor blood on hand.
- (c) Some metabolism occurs in the tissues during the course of profound hypothermia, and it is fairly marked during the rewarming period. The evidence for this is the arterio-venous oxygen difference present, particularly during rewarming; the relatively high venous carbon dioxide level present during bypass, despite efficient elimination by the oxygenator, and the presence of arterio-venous carbon dioxide differences during the procedure; and finally, the occurrence of some degree of metabolic acidosis after the

procedure. In addition, in one dog, marked metabolism occurred even during the cold period. This all indicates that at least low flows of oxygenated blood are necessary during profound hypothermia, and that total cessation of circulation might be hazardous. As a result, the use of an artificial oxygenator in the circuit is advocated when inducing profound hypothermia, in preference to the use of the autogenous oxygenation technique, where total cessation of circulation is normally employed.

- (d) Only insignificant changes occurred in venous pressure, and no change occurred in the sodium and chloride levels. As a result, it is felt that these parameters do not require further investigation.
- (e) The efficiency of the bubble oxygenator is indicated by the high arterial oxygen saturations during bypass. One disturbing aspect, however, is the high haemolysis that occurs with the use of this oxygenator. This is probably an indication that some other oxygenator should be used in performing cardio-pulmonary bypass with profound hypothermia.
- (f) The basis of the safety of hypothermia - the reduced oxygen requirements shown by Bigelow - are again demonstrated. During warming, however, there is an increase in oxygen requirements. The possibility that this is due to pooling of
blood /....

blood in certain tissues during the cold phase is discussed. It is consequently felt that, during rewarming, somewhat higher flow rates than are generally used, should be employed.

- (g) The necessity for administering small doses of sodium bicarbonate to counteract the mild metabolic acidosis that occurs, is demonstrated.
- (h) The fall that occurs in the potassium levels during the bypasses is discussed and the necessity for further investigation of this aspect is shown.
- (i) Finally, despite the changes which occur in the "milieu interieur" of dogs during profound hypothermia, its inherent safety when associated with an extracorporeal circulation, in the form of the bubble oxygenator, is demonstrated by the return to pre-bypass levels of the parameters studied, almost immediately after the procedure.

* Manufactured by Kipp, Delft, Holland.

** Manufactured by Metrohm Ltd., Herisau, Switzerland.

*** Manufactured by Beckman Instruments, Inc.,
Fullerton, California, U.S.A.

CHAPTER FOUR.

CHAPTER FOURTHE CLINICAL USE OF PROFOUND HYPOTHERMIA WITH
THE BUBBLE OXYGENATOR.SECTION A - INTRODUCTION.

The culmination of this research work in profound hypothermia came on Thursday, 16th June, 1960, when the technique incorporating profound hypothermia with the bubble oxygenator was first used on a patient in Cape Town. This occurred before the completion of the experimental series described in Chapter Three as, at that time, it was already established that the technique was a useful and necessary aid to cardiac surgery. Its actual clinical use served to confirm this and since then all the more difficult cases subjected to cardiac surgery have been performed with the aid of this procedure.

With a view to emphasising its usefulness and safety again, the initial clinical application of the technique will be described, prior to drawing the final conclusions. The method which has been evolved on the basis of the experimental work will be dealt with first, and the patients themselves will then be briefly discussed. A few changes that occurred in various parameters during the procedure will also be mentioned, as it is felt that it is only by the observations of such variables by many workers, and the subsequent correlation of their findings, that the ultimate aim, the complete understanding of man rendered profoundly hypothermic, will be attained.

Section B /....

SECTION B - MATERIAL AND APPARATUS.

This series includes the first 25 consecutive patients, all of whom suffered from various congenital or acquired cardiac defects, operated on between the 16th June and 18th October, 1960, with the aid of this technique. As has already been mentioned, the application of this technique was reserved for the more difficult cases only. The reason for this was that over 120 cardiac cases had been subjected to cardiopulmonary bypass using the bubble oxygenator under normothermic conditions in the past, with excellent results, and thus it did not seem justifiable to use an unknown procedure for cases such as atrial septal defects, isolated pulmonary stenoses, and some of the uncomplicated ventricular septal defects.

In Figure IV, 1, it can be seen that the material has been divided into two groups. This has been done to enable a more accurate assessment of the safety and usefulness of profound hypothermia to be made. In the first group appear the cases in which anatomical correction of the defect was possible at operation (Group I). The second group comprises 6 of the 25 cases, and in these the nature of the defect rendered an anatomical repair impossible by the techniques in cardiac surgery available and in use at that time (Group II).

The lesions presented in Group I were mainly tetralogy of Fallot malformations and ventricular septal defects, especially those associated with a pulmonary infundibular stenosis. Three of the cases had acquired aortic valvular disease. The patients' ages varied between 15 months and 31 years, with an average of 15½ years, and the weights between 2.3 kilograms and 82 kilograms.

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GROUP I.

LESIONS ANATOMICALLY REPARABLE BY PRESENT TECHNIQUE.

No.	Case	Race/Sex/Age	Weight in kg.	Lesion	Flow Rates ml. per min.		Lowest mid- oesophageal temp. in C.	Duration of bypass in mins.	Outcome
					Min.	Max.			
1	J.F.	EM 5½ yrs.	15	Tetralogy of Fallot	880	1536	15	113	Survived
2	D.N.	EM 15 "	50	V.S.D. + Pulm. infund. stenosis	1000	3250	18	72	"
3	I.P.	EM 21 "	64	V.S.D. + Pulm. infund. stenosis	1000	3822	18	85	"
4	P.N.	EP 4 "	12	V.S.D.	800	1320	19	92½	"
5	M.N.	CM 14 "	45	V.S.D. + Pulm. infund. stenosis	1672	2940	20	93	"
6	B.B.	CM 22 "	65	V.S.D.	1760	3700	17	67	"
7	M.N.	EM 23 "	50	Tetralogy of Fallot	1760	3255	17	126	"
8	B.S.	EM 15 mnths.	2.3	Tetralogy of Fallot	600	1150	17	41	"
9	D. du P.	EM 30 yrs.	82	V.S.D. + Pulm. infund. stenosis	1200	3870	19	131	Died
10	G.E.	EM 4½ "	16	V.S.D. c. pulm. hypertension	880	1800	16	73	Died
11	P.N.	EP 31 "	53	Acquired A.S. + A.I.	1000	2700	14.9	97	Survived
12	A.S.	EM 8 "	18	Tetralogy - re-op. on V.S.D.	1000	2100	14.4	57	"
13	G.P.	EM 31 "	"	Calcific A.S. + A.I.	1269	3710	14.8	240	Died
14	J.B.	EM 27 "	59	V.S.D. + Aortic incompetence	1800	3650	15	120	Survived
15	A.v.R.	EP 20 mnths.	8	Ideopathic pulmonary hypertension	700	960	24	70	"
16	V.M.	CM 3 yrs.	9	Tetralogy of Fallot	440	1200	17	117	"
17	M.S.	EP 9½ "	23	V.S.D. + P.D.A.	800	2118	17	130	"
18	C. McL.	CF 30 "	50	A.S. + Mitral Incompetence	1000	3150	19.1	128	"
19	A.C.	CM 12 "	23	Tetralogy of Fallot	700	2000	18	85	"

GROUP II.

LESIONS ANATOMICALLY IRREPARABLE BY PRESENT TECHNIQUE.

No.	Case	Race/Sex/Age	Weight in kg.	Lesion	Flow Rates ml. per min.		Lowest mid- oesophageal temp. in C.	Duration of bypass in mins.	Outcome
					Min.	Max.			
1	M.S.	EM 40 yrs.	41	Tetralogy of Fallot. Hypoplastic pulmonary artery.	1320	3000	18	176	Died
2	M.C.	EP 9 mnths.	2.3	Complete B.C.D. c. both PA's and aorta arising from one ventricle. Hypoplastic pulmonary artery.	300	600	16.1	114	Died
3	S.M.	CF 1 year	2.4	Tetralogy of Fallot. Hypoplastic pulmonary artery.	Pump off	480	14	58	Died
4	S.J.	CF 8 yrs.	15	Tetralogy of Fallot c. hypoplasia of MPA and branches	600	1600	16.4	234	Died
5	L.K.	CF 14 days	3	Epstein's anomaly c. 2 ost. sec. atrial septal defects + large P.D.A.	520	700	14	61	Died
6	J.S.	EM 3 mnths.	4	Transposition of great vessels and patent foramen ovale	Pump off	480	10	74	Died

FIGURE IV, 1.

Results obtained with the first 25 patients subjected to profound hypothermia with cardiopulmonary bypass utilising the bubble oxygenator. These patients have been grouped into anatomically reparable and anatomically irreparable lesions.

Erratum: Group I, No. 8 (B.S.) minimum flow rate should be "Pump off".

The second group includes anomalies such as transposition of the great vessels, Ebstein's anomaly, tetralogy of Fallot with pulmonary arterial hypoplasia and multiple cardiac lesions. The ages of the patients in this group varied between 14 days and 40 years, and the weights between 2.3 kilograms and 41 kilograms.

The cardiopulmonary bypass apparatus used in all these cases consisted of the DeWall-Lillehei helix reservoir bubble oxygenator, with Bennington heat exchange units placed in the arterial line, and was exactly the same as the setup used for the dog experiments (See Chapter Three, Section B and Figures III, 5 to 8). The number of heat exchange units employed depended on the size of the patient; for patients weighing up to 20 kilograms, a single unit proved sufficient; for patients between 20 and 40 kilograms, it was found that two units were required; for patients weighing over 40 kilograms, three units were used.

During the bypass, temperatures were recorded in the mid-oesophagus, in the rectum and in the blood leaving the patient and leaving the heat exchange units, using the Electric Universal Thermometer, as in the dogs. The E.C.G., and venous and arterial or line pressures, were recorded on a multichannel recording unit.

SECTION C - METHODS.

(1) The Preparation of the Bypass Apparatus:

In these patients, the preliminary preparation of the apparatus, its sterilisation by autoclaving and its assembly on the morning of procedure, were exactly the same as has been described for the dogs, with the exception that the actual assembly of the apparatus, under sterile conditions, was performed by a

doctor /....

doctor and not by a technician. Once assembled, the initial priming with saline, the debubbling, the calibration and pump occlusion testing, and the final priming of the apparatus with the donor blood, were all exactly the same as for the dogs (See Chapter Three, Section C, (1)).

The arterial pump was calibrated so that "full flow" rates could be delivered during the active cooling and warming phases. These flow rates were estimated on the basis of 2.4 litres per square metre per minute for the patients with a body surface area of up to 1 square metre, and for those with a greater surface area, 2.1 litres per square metre per minute. The pump was also calibrated so that flow rates of two-thirds, one half and one-third of the calculated "full flow" rate could be delivered during the cold or static phase, while the intra-cardiac operation was being performed.

(2) The Operative and Bypass Procedures:

The usual procedure used in the clinical cases is briefly as follows. It is essentially similar to that used in the dogs, with certain necessary modifications.

Anaesthesia is induced with thiopentone sodium, or with fluothane, and is maintained with ether or fluothane. During the hypothermic phase, no anaesthetic agents are necessary because of the "cold narcosis" that ensues.

The patient is positioned on the operating table, the E.C.G. leads are connected and the mid-oesophageal and rectal temperature leads are inserted. A left femoral cut-down is performed and a thin polyethylene catheter is inserted via the saphenous vein into the inferior vena cava, to enable the venous pressure to be recorded and blood samples to be collected.

The exposure of the heart for the operation, unlike that in the dogs, is obtained by means of a median sternotomy, and the preparation of the heart for bypass differs in that both venae cavae are taped, as for a normothermic bypass (Barnard et al, 1959). After the patient has been heparinised, the right common femoral artery is cannulated, as in the dogs, with a metal catheter of a size adequate to carry the arterial flow, but without creating a pressure gradient across the catheter of greater than 70 to 100 mms. of mercury. (In babies of under eighteen months of age these two preparatory procedures differed. Firstly, it was found that the common femoral, the external iliac and the common iliac arteries were all too small to take a catheter of adequate internal diameter, and thus the arterial catheter was inserted through the ascending aorta, with the tip pointing towards the aortic valve. Secondly, in some of these babies, the venae cavae were not taped. Subsequently, in these cases, a single catheter only was inserted into the atrium and full flow partial bypass with cooling carried out exactly as in the dogs).

The preparation of the arterial and venous lines, the connection of the patient to the bypass apparatus and the commencement of the bypass are all similar to the technique used in the dogs. In the patients, however, with the exception of some of the babies mentioned above, both venae cavae were catheterised through the right atrial appendage (see Figure III, 5) and the catheters were secured by means of a Romell clamp. In addition, as soon as bypass is begun, the venae caval tapes are tightened and the patient's heart is completely bypassed. At this stage the bypass is at the full calibrated flow rate. This cooling on complete bypass with "high flow" rates is quite different from the technique employed in other centres, where

low /....

low flow partial bypass is usually employed.

During the early stages of cooling, the heart usually is opened and the operative procedure commenced. As cooling progresses the heart begins to fail, or ventricular fibrillation occurs. At this point decompression of the left heart is necessary to prevent its over-distension by the blood returning via the bronchial collateral vessels. In the cases where a septal defect is present the decompression is usually performed via a catheter placed through the cardiotomy and through the defect. In other cases it is performed through the left atrium by means of a catheter which has been inserted from the right side of the mediastinum through the wall of the left atrium, or through a pulmonary vein.

When the mid-oesophageal temperature reaches about 20 degrees centigrade, the flow is reduced and then maintained at this reduced rate throughout the hypothermic phase, unless for some reason (to facilitate surgery) the bypass is stopped completely. The flow is usually reduced to one-third of the calculated "full flow", but in some cases one-half (Figure IV, 2) or two-thirds of the "full flow" is used. At this stage, cooling is still progressing but, when the desired level of hypothermia is reached, the temperature is kept more or less constant by allowing the blood to flow either through the heat exchange units or through the special line bypassing the heat exchange units (Figure III, 5), as required. The low flow rates used during the hypothermic phase reduce the amount of blood returning into the heart, via the coronary sinus and bronchial collaterals, to an extent where its volume does not obscure the operative field and hamper surgery. At this stage, it is easily handled by means of a small intracardiac sucker. Thus flow is allowed through the coronary vessels throughout the operation, except during the actual tying of sutures in a ventricular septal defect's repair, when a completely relaxed heart is necessary.

During /....

During this phase, the aorta is cross clamped. The aorta is also cross-clamped during surgery on the aortic valve, with or without the use of coronary arterial perfusion.

The details of the actual surgical procedures performed in these cases will not be dealt with as they are beyond the scope of this thesis.

The change-over to warm water and the commencement of rewarming are performed in the same way as in the dog experiments. To save time, the aim is to begin rewarming the patient about 10 minutes before the completion of the intracardiac repair. During rewarming the flow is usually rapidly increased again until a "full flow" rate is reached, thereby shortening the time required to rewarm. At this stage, a small dose of 4 percent sodium bicarbonate, mixed with an equal volume of 50 percent glucose, is given to counteract any metabolic acidosis present.

When the mid-oesophageal temperature reaches between 32 and 36 degrees centigrade, if spontaneous reversal to sinus rhythm does not occur, electric shock defibrillation is employed and is usually easily accomplished, with few exceptions. The heart beat is first restored before the cardiectomy wound is completely closed to permit decompression of the non-beating heart with the cardiectomy suckers, thus avoiding over-distension of the relaxed myocardium. At this stage the bypass is discontinued, as in a normothermic bypass, and the atrial catheters are removed.

Once again, as in the dogs, the patient's blood balance is estimated using the arterial and venous pressures as monitors in preference to the use of the actual estimate of blood loss made. Any blood deficit is replaced via the arterial catheter. The required dose of "polybrene", to neutralise the heparin, is then administered.

The heart and pericardium are carefully inspected for any bleeding and the pericardium is approximated. A false communication is made between the anterior mediastinum and the right chest and then the pericardium and right chest are drained with catheters attached to special suction pumps. The chest wound is closed in layers, using wire for the sternum in adults and catgut in babies. The femoral artery catheter is removed, the arteriotomy is repaired with a continuous atraumatic 5 or 6 "0" black silk suture, and finally the right femoral wound is closed.

(3) The Postoperative Period:

After the completion of the operative procedure, the patient is returned to a specially equipped cardiac recovery ward. A detailed post-operative care routine is instituted as is done with the normothermic cardiopulmonary bypass cases. The patient is continuously "specialized" by a team consisting of a doctor and nursing staff until the next morning, and then by nursing staff alone for up to one week after the procedure. Antibiotic therapy is instituted immediately and restricted fluids are administered overnight. Blood drainage is replaced, volume for volume, with whole citrated blood as it occurs. A further dose of sodium bicarbonate is also usually given at this stage. Digitalis is administered where necessary, as are other cardiac drugs.

Further details of the post-operative care and the later follow up of these patients is beyond the scope of this thesis.

(4) Biochemical Estimations:

The details of the techniques used in the special investigations will be dealt with in the appropriate Section.

The postoperative plasma haemoglobin was measured by the method described by Crosby (Crosby and Furth, 1956).

As in the experiments with dogs, the pH determinations were made using the "Metrohm Electrodes for Blood pH", the venous carbon dioxide saturations were measured using the method of van Slyke (Peters and van Slyke, 1932), and the venous oxygen saturations were measured using the "Brinkman Haemoreflector".

SECTION D - GENERAL RESULTS AND DISCUSSION.

Having dealt with the methods used in these clinical cases, a few of the changes that occurred in some parameters during the procedures will now be discussed. These will be dealt with briefly, with the main object to confirm the findings in the dog experiments.

Some of the results obtained in the 25 patients that constitute this series are tabulated in Figure IV, 1, and the nature of the actual lesions found at operation is summarised. Figure IV, 2, is a graph depicting some of the bypass details in Case 1, Group I.

(1) Survival:

It can be seen from Figure IV, 1, that the cases have been divided into two groups (see page 132). This was done to more accurately assess the survival rate.

- (a) Group I: This group includes all the cases in which anatomical correction of the defect was possible by surgery. In the 19 cases there were 3 deaths (16.7 percent) and thus the immediate survival rate was 83.3 percent.

The death in Case 9 was due to a pulmonary embolus. This occurred on the 9th postoperative day, while the patient was being treated for postoperative oliguria, but was quite unrelated to the oliguria. Case 10 had a tracheotomy performed early in the postoperative

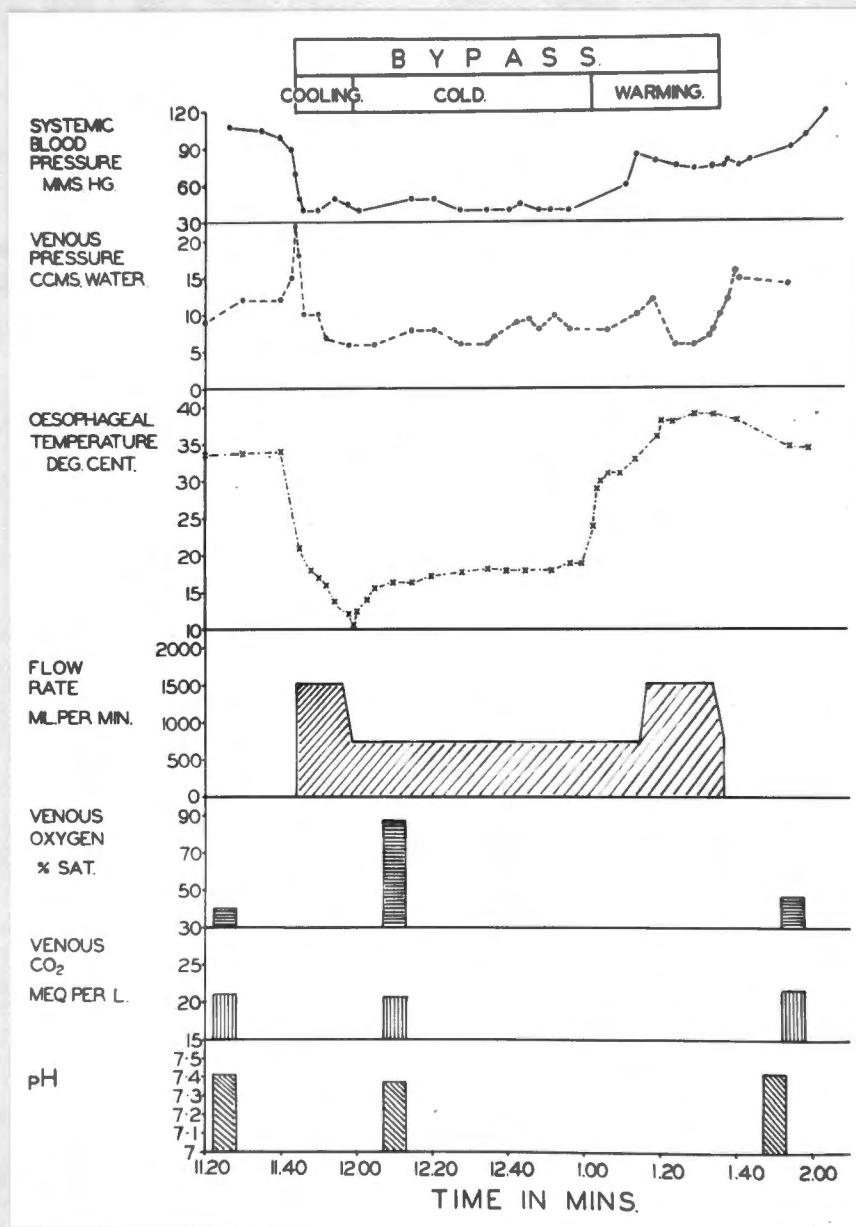


FIGURE IV, 2.

A graph showing the results obtained in case No. 1 (J.P.) of Group I (see Fig. IV, 1).

period to deal with excessive bronchial secretions. Mild wound sepsis ensued and on the 10th post-operative day a fistula developed between the tracheotomy wound and the mediastinum. The patient died 24 hours later from an undetected air tamponade. In Case 13 an attempt was made to correct a calcific aortic stenosis with incompetence and the patient died during surgery from aortic incompetence.

It is thus evident that none of these deaths were attributable to profound hypothermia, a definitely unrelated cause of death being present in all three. This, in conjunction with the 83.3 percent early survival rate confirms the opinion that profound hypothermia, induced as described, is a safe procedure for use in patients at it is in dogs.

- (b) Group II: This group includes the 6 cases where the nature of the defect rendered a surgical repair impossible by means of the techniques in cardiac surgery available and used at that date. The mortality was, of course, 100 percent.

It is understandable, from the nature of the lesions present in cases 2, 5 and 6, why they are included in this Group. In addition, 3 cases

with /....

with tetralogy of Fallot malformation associated with hypoplasia of the main pulmonary arteries are also included. The reason for this is that, in this type of case the complete correction in a single operation is not possible. Since this was realized and the procedure recommended by Brock - namely a two stage correction - was adopted (Brock, 1959), two patients have been subjected to the first stage of the procedure with, so far, excellent results (Cases 8 and 16 in Group I).

As with Group I, none of the deaths can be attributed to the technique of hypothermic perfusion employed. This constituted further confirmation of the safety of the technique described.

(2) Flow Rates:

Figure IV, 2, shows a typical example of the variation in flow rate that was employed. The patient was cooled using a calculated "full flow" and when hypothermic, the flow was reduced to one-half. The flow rate was kept at this level until shortly after rewarming had begun, when it was again increased to a "full flow" rate.

The actual full flow rates and reduced flow rates that were used are tabulated in Figure IV, 1. In 9 of the patients the flow was reduced to about one-half, in another 9 to about one-third, in 2 to about two-thirds, in 1 to three-quarters, and in 1 to about one-quarter of the full calculated flow, during the hypothermic phase. In addition, the flow was completely switched off in 3 cases (Case 8, Group I, and Cases 3 and 6, Group II).

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In Case 8, Group I, although the circulation was completely switched off, this did not seem to affect the patient adversely in any way. This confirms the finding in the experimental series, that although it is preferable to maintain a flow during hypothermia, complete cessation of circulation is compatible with survival. This ability to stop circulation completely is one of the safety factors of the technique. Should the bypass apparatus fail for any reason while the patient is hypothermic, the bypass can be stopped to allow repairs to be made.

The low flow rates used during the hypothermic phase reduces the amount of blood returned to the heart from the bronchial collaterals and coronary sinus to the extent where the return can be handled easily by a small intracardiac cardiotomy sucker. This is one of the major advantages of profound hypothermia with extracorporeal circulation, as the operative procedure is performed unhurriedly, in a virtually bloodless field, and surgery is thus considerably simplified.

A "high flow" rate is used during cooling and rewarming. This increases the rate of heat exchange and is, in fact, responsible for the shortness of these periods. In addition, a "high flow" rate during rewarming is probably advantageous because of the increased metabolism that was shown to occur during this phase in the experimental series with dogs.

(3) Temperatures:

Figure IV, 2, shows the usual variations that occurred in the mid-oesophageal temperature during the procedures. The degree of hypothermia employed usually depended on an estimate of the complexity of the repair. The lowest mid-oesophageal temperature

recorded /....

recorded in all the cases (with two exceptions) was between 14 and 20 degrees centigrade (Figure IV, 1). As no repair was required in case 15, Group I, because it turned out to be an idiopathic pulmonary hypertension, the temperature was not reduced below 24 degrees centigrade. As the circulation in Case 6, Group II, was going to be switched off for some considerable time, the temperature was reduced to 10 degrees centigrade, and in fact, although the patient was on bypass for 74 minutes only, the circulation was stopped for 104 minutes.

The ease with which low temperatures are attained once again indicates the efficiency of the system of heat exchange employed.

Rectal temperatures were taken in addition in all the cases at the same times as the mid-oesophageal temperature was measured. The wide variation between these temperatures confirmed the findings in the dog experiments.

(4) Arterial and Venous Pressures:

No significant variation in venous pressure was noted during these perfusions. An example can be seen in Figure IV, 2. The temporary elevation at the point of going on bypass was due to unsatisfactory venous drainage, and this was soon overcome.

A typical arterial pressure variation is also demonstrated in Figure IV, 2. It can be seen that the fall in blood pressure occurred before the flow rate was reduced. In all the cases, the blood pressure rose with rewarming.

The pattern of variation is similar to that occurring in the dogs and the same possible etiology must apply.

(5) The Heart:

In all the cases, ventricular fibrillation occurred as the

temperature dropped below 25 degrees centigrade. As occurred in the dogs, with a further reduction in temperature the ventricular fibrillation became less vigorous and less forceful. It usually continued throughout the static phase, and complete arrest only occurred in the cases in which bypass was stopped or the aorta was cross-clamped.

A quiet heart, to facilitate the operative procedure, can thus be obtained without the use of drugs or normothermic anaesthesia. This avoids the deleterious effects that have been shown to ensue after chemical arrest (Gott et al, 1959), and this represents another advantage of profound hypothermia in cardiac surgery.

(6) The Length of Perfusion:

The average length of actual bypass in these cases was 106 minutes (Figure IV, 1).

The fairly long perfusions indicate the complexity of most of the lesions operated on using this procedure. In addition, some of the time on bypass is used solely to cool and rewarm, thereby further increasing the length of the perfusions. This, however, can be reduced to a minimum by careful planning.

(7) Blood Destruction during the Procedure:

In this series the postoperative plasma haemoglobin (an estimate of the blood destruction in the apparatus) averaged 115.6 milligrams percent. It has already been mentioned that the average length of perfusion was 106 minutes. The average blood destruction that occurred was thus in the region of 1 milligram of plasma haemoglobin present for each minute of bypass. When discussing the dog experiments it was mentioned

that during normothermic perfusions of patients in the past, using the bubble oxygenator, a haemolysis figure of about 1 milligram of plasma haemoglobin for each minute of bypass was customary. In the dogs it was shown that this haemolysis became progressively higher as the perfusion was continued.

The finding of a similarly high haemolysis figure in this series further confirms the opinion that the bubble oxygenator is the cause of this high haemolysis, and that some other oxygenator might be preferable when using the technique, especially for prolonged bypasses.

(8) pH Determinations:

These were undertaken in a few of the cases, on arterial blood samples, and were measured and recorded as in the dogs at 38 degrees centigrade.

Figure IV, 2, is an example of a case where pH determinations were made. It can be seen that the pH of the blood taken during hypothermia and recorded at 38 degrees centigrade dropped only very slightly. The pH of the blood taken after the bypass was normal. This was the case with all the estimations made. As occurred in some of the dogs, the patients were all given a small dose of sodium bicarbonate during rewarming.

It is felt that the only significant pH reading is the final one, taken when normal body temperature is again present. The fact that this reading is normal indicates two things: firstly, that no major disturbance of acid-base equilibrium takes place as a result of the procedure and, secondly, that the small dose of sodium bicarbonate given is beneficial, apparently. This again confirms the findings in the dog experiments.

(9) Venous Carbon Dioxide:

Figure IV, 2, indicates the levels of venous carbon dioxide during one of the perfusions. This parameter was measured in 21 of the 25 cases. During and after the procedure it fell to below 40 volumes percent in only 6 of the cases, and in only 1 of these was the level below 35 volumes percent. The average pre-bypass control level was 47.2 volumes percent, mid-bypass level was 44.7 volumes percent and the immediate post-bypass level was 42.4 volumes percent.

The efficiency of the bubble oxygenator in eliminating carbon dioxide has already been mentioned. The fairly high venous carbon dioxide levels during the hypothermic phase of the bypasses indicates that metabolism is taking place in the tissues, thereby producing carbon dioxide to replace that eliminated by the oxygenator. This adds confirmation to the finding in the dogs that even at low temperatures some tissue metabolism takes place, and emphasizes the necessity for maintaining a perfusion throughout the procedure.

In addition, the final carbon dioxide level, after bypass, was relatively high. If this is considered in conjunction with the relatively normal pH at that time, it indicates that minimal metabolic acidosis occurs as a result of the procedure and confirms this finding in the dogs. It constitutes a further advantage in using profound hypothermia for difficult cases, as prolonged normothermic perfusions are associated with the occurrence of a metabolic acidosis (Kelff, Effler and Greves, 1960).

(10) Venous Oxygen Saturation:

This was estimated in 21 of the 25 cases. Figure IV, 2, shows the venous oxygen saturation levels in one of the cases. The high

venous /....

venous oxygen saturation that was present during the bypass is clearly demonstrated. Similar high levels occurred during the bypasses in most cases, and in 13 of the patients the level was above 70 volumes percent of oxygen.

This confirms the finding in dogs that, with exceptions, there is little oxygen demand by the body during profound hypothermia.

In 8 of the cases, however, the venous oxygen saturation during the bypass was below 70 volumes percent, and in 3 of these it was below 40 volumes percent, the lowest value being 33 volumes percent.

As the bubble oxygenator fully oxygenates the blood passing through it, this finding of low venous oxygen saturations confirms the single dog experiment in which a fairly high demand for oxygen was found, despite the hypothermia. The disturbing factor is that these cases cannot be predicted. A perfusion of at least low flows of oxygenated blood should be maintained through the course of profound hypothermia, thus, to make oxygen available in the few cases where there is a large demand. In addition, this would meet the small oxygen requirements normally present during hypothermia. It is further evidence against the total cessation of circulation, except for short periods when it is essential to facilitate surgery.

(11) Renal Failure:

Two cases in this series (Cases 9 and 14, Group I) developed the signs of acute tubular necrosis postoperatively. Case 9 died with a pulmonary embolus (unrelated cause) before his renal failure had had a chance either to recover or to become severe, and Case 14 has subsequently made a complete recovery.

In the literature to date there is one report of acute tubular necrosis occurring during such a procedure (Gerbode, Osborn and Johnston, 1960, a). It was demonstrated in the experiments with dogs that, although renal function is disturbed by the procedure, it returns to control levels during rewarming, and remains there, immediately afterwards. The possibility exists, of course, that the renal failure in these patients was due to some cause other than the hypothermia, but this cannot be proven.

In 120 prior cases subjected to normothermic perfusions in Cape Town, no case of this complication occurred. Therefore, despite the dog findings, the possibility of tubular necrosis being a danger in this type of hypothermia must be contemplated. Further work in this field is at present being undertaken. It is the writer's conviction, however, on the basis of the experimental work, that hypothermia per se does not endanger the kidney.

(12) Postoperative Bleeding:

In these cases, postoperative bleeding was a more troublesome feature than it was with normothermic bypasses performed in the past, and 3 patients had to be taken back to the theatre in order to control the bleeding. In addition, the bleeding in these 3 cases commenced several hours after the completion of the operation.

The reason for this is at present still obscure, and it is one aspect of profound hypothermia with cardiopulmonary bypass that should be investigated further.

(13) Conclusions:

During the discussion of the changes which took place during the perfusions in the first 25 cases subjected to profound

hypothermia with cardiopulmonary bypass in Cape Town, the following important points came to light:-

- (a) Profound hypothermia, induced as described, is a safe technique. This is indicated by the 83.3 percent survival rate in Group I, where the lesions were repairable, and the fact that none of the deaths were due to the hypothermia per se. An additional safety factor is that, should a technical hitch occur with the bypass apparatus during hypothermia, it is possible to stop the circulation and attend to the trouble. The dangers of chemical arrest of the heart are also avoided as the hypothermia itself induces a quiet heart.
- (b) Surgery is facilitated as the low flow rates employed ensure a virtually bloodless operative field, and a quiet heart is produced by the hypothermic fibrillation or arrest that ensues.
- (c) The heat exchange system described is efficient as indicated by the ease with which low temperatures are attained. The rapid cooling and warming are aided by the "high flow" rates employed.
- (d) At least some tissue metabolism occurs, despite profound hypothermia, as the venous carbon dioxide levels during this phase are high even in the presence of efficient elimination by the oxygenator. In most cases, this metabolism is, however, minimal, as evidenced by the high venous oxygen levels during hypothermia. In some cases, which are unpredictable, greater /....

greater tissue metabolism takes place, as evidenced by the relatively low venous oxygen levels that occur at times during hypothermia.

- (e) A low flow perfusion rate is safe during hypothermia as the venous oxygen saturation is usually high, despite the low flow, and its use is associated with a good survival rate. Although complete cessation of circulation may be employed safely when essential, a low flow of oxygenated blood is preferable as metabolism does occur in the cold tissues and in some cases it is fairly marked.
- (f) No major disturbance in acid base balance is present, despite prolonged perfusions. The fact that no marked metabolic acidosis occurs is evidenced by a normal pH after the procedure, in conjunction with a relatively high venous carbon dioxide level. The small dose of sodium bicarbonate administered during the warming apparently counteracts any minimal acidosis that might be present.
- (g) The venous pressure variations are not significant and the blood pressure variations are similar to those which occurred in the dogs, probably for the same reasons.
- (h) The lengthy perfusions indicate the complexity of the cases operated on in this series.
- (i) The technique has certain possible disadvantages and dangers. The high haemolysis that occurs is a possible danger and may be an indication for the use of another oxygenator in preference to the bubble oxygenator. Although renal failure occurred in 2 patients, it is felt that hypothermia does not endanger the kidney, as evidenced by the dog

experiments, but the possibility of this danger should be borne in mind. The question of increased postoperative bleeding requires further investigation. Although the length of time of perfusion is increased by the cooling and rewarming time, this disadvantage can be made less important by careful planning.

- (j) Finally, the use of profound hypothermia with the bubble oxygenator, induced as described in these 25 patients, has demonstrated very clearly its usefulness, safety and necessity as an aid to cardiac surgery today, especially in the more difficult cases.

SECTION E - AN INVESTIGATION OF THE PLASMA CORTISOL, POTASSIUM AND GLUCOSE LEVELS DURING AND AFTER THIS PROCEDURE.

" This study was undertaken as a result of interest in the metabolic and other changes that occur in patients during the application of profound hypothermia with cardiopulmonary bypass. The results are recorded here as they are felt to be of help in filling another gap in the understanding of what happens to the profoundly hypothermic man, thereby eventually leading to the safer application of the technique in the future.

Richard DeWall has investigated the changes that occur in cortisol, potassium and glucose in patients subjected to normothermic cardiopulmonary bypass using the bubble oxygenator. His method of performing normothermic cardiopulmonary bypass was similar to that used in Cape Town. During his bypass, he

showed /....

HYPOTHERMIC BYPASS CASES					
Patient / Weight Sex / Age	Lesion at operation	Flow Rates in ml. per minute		Lowest mid- oesophageal temperature	Duration of Bypass in minutes.
		min.	max.		
1. P.H. 12 kg F 4 years	Ventricular septal defect.	800	1320	19°C	92½
2. S.J. 15 kg F 8 years	Tetralogy of Fallot with hypoplasia of main pulm. artery and branches	600	1600	16.4°C	234
3. G.E. 16 kg M 4½ years	Ventricular septal defect with pulm. hypertension	880	1800	16°C	73
4. A.S. 18 kg M 8 years	Tetralogy of Fallot. Re-op. on ventricular septal defect.	1000	2100	14.4°C	57
5. A.v.R. 8 kg F 20 months	Ideopathic pulmonary hypertension	700	960	24°C	70
6. A.C. 23 kg M 10 years	Tetralogy of Fallot	616	2000	15.5°C	101
NORMOTHERMIC BYPASS CASES					
1. V.C. 26 kg F 10 years	Incomplete endocardial cushion defect.	-	2280	-	78
2. N.G. 15 kg M 4½ years	Ostium secundum atrial septal defect	-	1608	-	29
3. D.K. 21 kg M 8 years	Infundibular pulmonary stenosis	-	1896	-	64
CONTROL CASES					
1. H.van H. M 5 years	Patent ductus arteriosus	-	-	-	-
2. E.K. F 9 years	Patent ductus arteriosus	-	-	-	-

FIGURE IV, 3.

Results of studies on patients in
whom cortisol, glucose and potassium
were estimated.

showed a rise in glucose and a fall in potassium levels in the patients' blood, but found that only an insignificant rise occurred in plasma 17, 21 - dihydroxy - 20 - ketosteroids (DeWall, Warden, Melby, Minot, Varco and Lillehei, 1957, b), when measured by the Silber-Porter technique (Silber and Porter, 1954).

The aim was to investigate the changes that would occur in these parameters during profound hypothermia with the bubble oxygenator, and to see how these differ from the changes that took place during normothermic cardiopulmonary bypass.

(1) Material:

Eleven cases were selected at random for this study (Figure IV, 3). They were all children with congenital cardiac abnormalities admitted to the Red Cross War Memorial Children's Hospital. Six of them were subjected to cardiopulmonary bypass with hypothermia, and as they were among the first 25 cases subjected to this technique, they are included in the series already described (Figure IV, 1). Three other children were subjected to normothermic cardiopulmonary bypass only, and 2, who acted as controls, each had a patent ductus arteriosus repaired by surgery without the aid of either bypass or hypothermia.

(2) Methods:

The following venous blood samples were collected from the patients subjected to hypothermic and to normothermic cardiopulmonary bypass. The control specimens 1 and 2 were taken the day before operation, at 5.00 p.m., and on the morning of surgery at 9.00 a.m., respectively. A further

sample /....

sample (number 3) was taken when the thoracic cavity had been opened, but prior to commencing the bypass, at the stage when the heparin was given. Specimen 4 was taken half an hour after beginning the bypass, specimen 5 just before going off bypass, and specimen 6 in the post-bypass phase, while the chest was being closed. Specimen 7 was taken one hour postoperatively, specimen 8 at 12.00 midnight on the day of surgery, and specimen 9 at 8.00 a.m. the following day. In some cases, however, not all nine specimens were obtained.

In 3 cases a specimen was also taken from the pooled donor blood used to prime the bypass apparatus. The donor blood for all the patients was obtained on the morning of operation.

In the 2 control patients, the venous blood samples (except specimens 4 and 5) were obtained at similar times to the bypass cases. Specimens 4 and 5 were taken during the actual repair of the patent ductus arteriosus.

In all patients, samples 1 and 2 were taken from the anterior cubital vein, and the remainder were taken from the common iliac vein or lower inferior vena cava, by means of a polyethylene catheter, the tip of which was inserted into one of these vessels.

In the hypothermic and normothermic bypass cases, some 25 percent glucose was given intravenously with sodium bicarbonate, between the taking of specimens 4 and 5. The average amount of glucose given in each of the 9 cases was 10.75 grams. No potassium-containing solutions were administered.

Serum cortisol was measured by the Silber-Porter method, as modified by Peterson (Peterson, Karrer and Guerra, 1957), serum potassium by flame photometry and serum glucose as described by Varley (Varley, 1954).

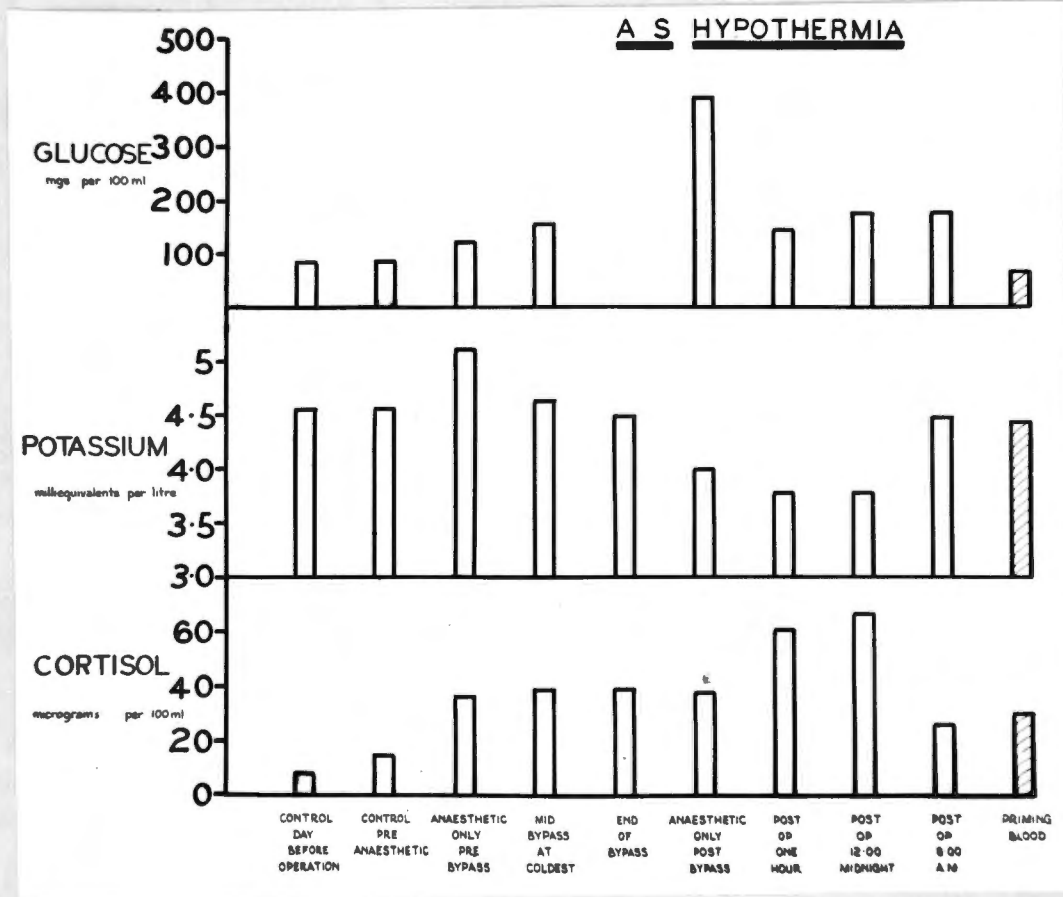


FIGURE IV, 4.

The cortisol, glucose and potassium levels in the fourth hypothermic bypass patient in whom these were estimated.

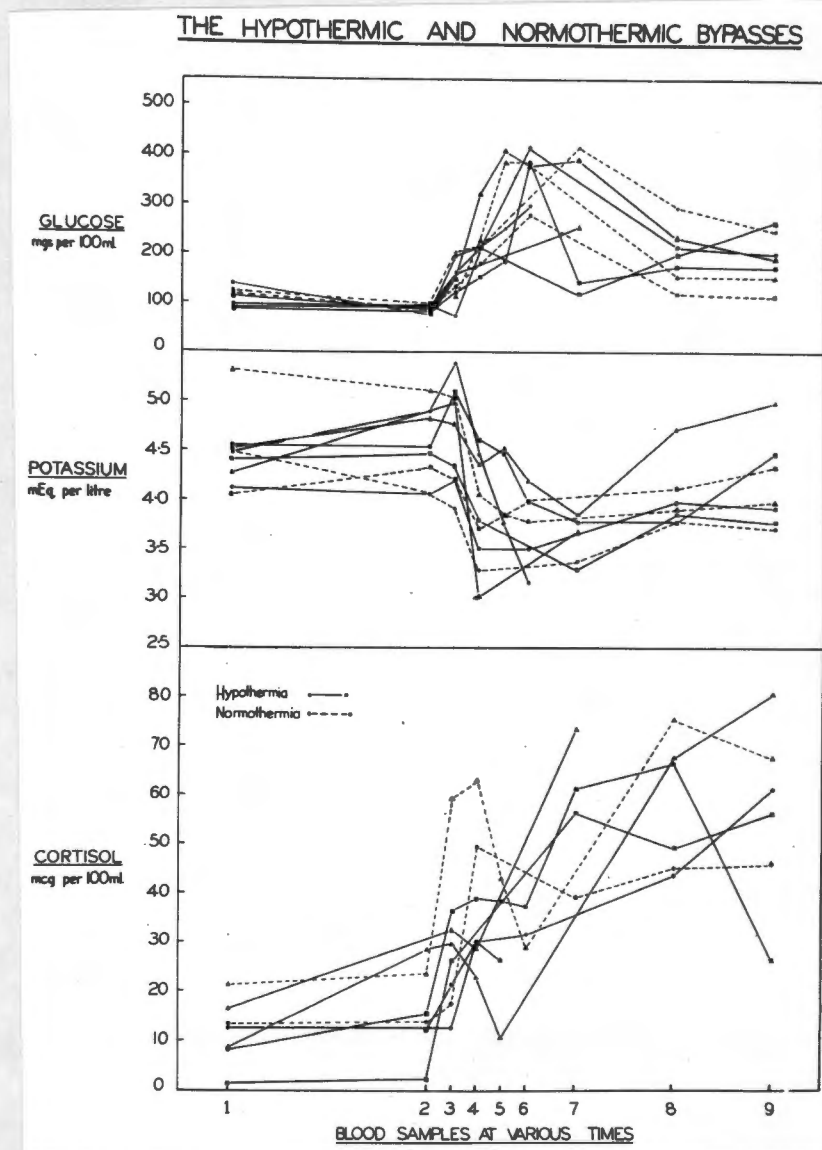


FIGURE IV, 5.

The cortisol, glucose and potassium levels estimated in all the hypothermic and normothermic bypass patients in whom these were studied.

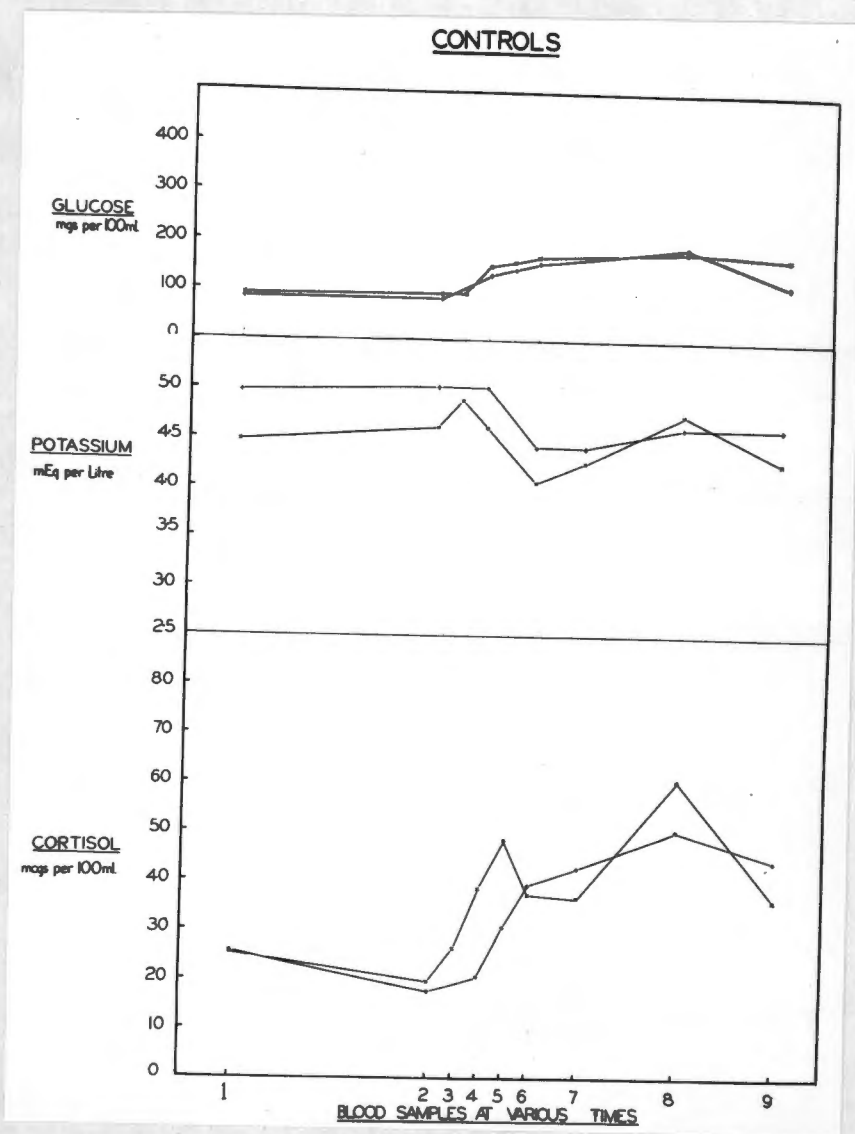


FIGURE IV, 6.

The cortisol, glucose and potassium levels estimated in the control cases.

(3) Results:

Figure IV, 3, shows the cases studied and lists some of the bypass details. Figure IV, 4, shows the variations in cortisol, glucose and potassium levels that occurred in one of the cases (A.S., hypothermic case No. 4). Figure IV, 5, is a composite graph showing the variations that occurred during and after the 6 hypothermic and the 3 normothermic cardiopulmonary bypasses. Figure IV, 6, is a similar graph showing the variations that occurred during the 2 control experiments where the patients were not subjected to cardiopulmonary bypass or to hypothermia.

In Figures IV, 5 and 6, although specimens 3 to 7 did not correspond exactly in time relationships, they have been superimposed as they correspond in relation to the bypasses themselves. Specimens 1, 2, 8 and 9 were, however, taken at exactly the same times in all cases.

It can be seen that cardiopulmonary bypass alone was associated with a rise in glucose and fall in potassium, irrespective of whether hypothermia was added or not, with both of these values returning towards pre-operative levels by the next day (Figures IV, 4 and 5). The rise in the glucose level had already commenced by the time specimen 4 was taken, long before any glucose was administered, and the extent and duration of the subsequent rise was greater than could be accounted for on the basis of the glucose administered, alone.

When the patient was not subjected to cardiopulmonary bypass, however, but merely to a thoracotomy, these changes in glucose and potassium did not occur (Figure IV, 6).

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On the other hand, the expected rise in serum cortisol which occurs during operations (Moore, 1959; Bagall, Bro-Rasmussen and Buus, 1960; Pekkarinen, 1960) and which occurred in a thoracotomy alone (Figure IV, 6) was also present to about the same extent in both the normothermic and the hypothermic cardiopulmonary bypasses (Figures IV, 4 and 5).

In the 3 cases in which the pooled donor blood was studied the glucose levels were 65, 77 and 88 mgs. percent respectively, with an average of 77 mgs. percent. The potassium levels were 4.45, 3.50 and 3.71 mEq. per litre, with an average of 3.88 mEq. per litre. The serum cortisol levels were 30, 15.8 and 10 micrograms per 100 ml. with an average of 18.6 micrograms per 100 ml. These normal values indicate that the blood used to prime the bypass apparatus was not in itself responsible for the changes that occurred in the various parameters studied.

(4) Discussion:

The variations that occurred in the glucose and potassium levels in these normothermic bypasses correspond to those shown by DeWall using a similar bypass technique (DeWall et al, 1957, b). The fact that these two parameters follow the same pattern of variation when hypothermia is added to the cardiopulmonary bypass is of interest in the light of the many complex metabolic changes brought about by the deeper levels of hypothermia. The reason for this similarity will probably only come to light in the future as the work of many investigators is correlated and the understanding of profound hypothermia consequently grows. Nevertheless, it is important to note that, in respect to glucose and potassium levels in the blood, profound hypothermia does not upset the patient's metabolic balance any more than cardiopulmonary bypass alone.

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It was pointed out that the rise in glucose level had commenced long before any glucose was administered, and that the extent and duration of the subsequent rise was greater than could be accounted for on the basis of the glucose administration alone. The rise is felt to be due to diminished utilisation and storage of this substance during the bypass. The return of the level towards control values by the next day indicates that the upset in glucose metabolism is a temporary event and is not harmful.

The fall in serum potassium level that occurred regularly during the hypothermic and normothermic bypasses is felt to be due to a shift of potassium into the cells, without actual potassium loss from the body, as the level returns towards control values by the next day, without the administration of potassium-containing solutions. In fact, in the past, an increase in heart muscle potassium has been demonstrated during surface hypothermia (Spurr and Barlow, 1959; Beavers and Rogers, 1959, b).

The rise in serum cortisol in the control experiments (Figure IV, 6) is as expected (Moore, 1959; Engell et al, 1960; Pekkarinen, 1960). In the normothermic bypass cases a similar rise was found (Figure IV, 5). This finding conflicts with DeWall's work, as he too, using the Silber-Porter method of estimation, found no significant rise. The reason for this is, once again, not at present clear.

The most interesting finding was that the change in cortisol that occurred during and after the profound hypothermic bypass was similar to the change that took place with normothermic bypasses, and also during intrathoracic operations alone.

Egdahl and his co-workers have shown a considerable drop in the minute corticoid output in adrenal venous blood in the dog during surface induced hypothermia down to between 28 and 25

degrees centigrade. They conclude from this that the corticoid response to trauma does not occur in hypothermia (Egdahl, Nelson and Hume, 1955). Bernhard showed subsequently that the peripheral blood corticoid levels (an indication of the "tissue hormone environment") did not fall, but actually rose or remained the same during similar hypothermic experiments in dogs and in 2 human cases. His group concludes, therefore, that the rise in peripheral corticoid levels during hypothermia was due to the reduced metabolic breakdown of these steroids, rather than to an increased adrenal output (Bernhard, McMurray, Ganong and Lennihan, 1956).

Even bearing in mind that there is a difference between surface induced hypothermia and that induced by means of an extracorporeal circuit, the work of these investigators suggests that, despite the similarity in the above results for corticoid levels, different mechanisms are at play in producing the increased levels in the peripheral blood during the hypothermic bypasses on the one hand, and the normothermic bypasses on the other. The ultimate effect is, nevertheless, to produce a similar "tissue hormone environment" in both groups of cases.

(5) Conclusions:

The conclusions one can draw from these results are only speculative. It is already abundantly clear that the human body can stand the insult of profound hypothermia and return to normal. Is it not possible that the body is able in some way to strike a new balance, as occurs here, and that this is partly the basis of the safety of a technique which, at first glance, appears to be extremely hazardous?

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The rise that takes place in the glucose level is felt to indicate diminished utilisation and storage of this substance. The fall in potassium is felt to be due to a shift into the cells during the procedure, with a subsequent return of potassium into the plasma after the bypass.

The rise in the serum cortisol, despite evidence that hypothermia diminishes the output of this substance (Egdahl et al, 1955), is apparently due to a reduced metabolic breakdown.

There is little doubt that many further investigations similar to the above will have to be undertaken in various parameters during profound hypothermia, before the ultimate aim of a complete understanding of the profoundly hypothermic man can be attained.

CHAPTER FIVE

CHAPTER FIVE.A SUMMARY OF THE SIGNIFICANT FINDINGS AND CONCLUSIONS.SECTION A - INTRODUCTION.

In concluding this study of profound hypothermia with extracorporeal circulation and the bubble oxygenator, with special reference to its application in cardiac surgery, it is fitting to quote some very apt statements recently made by Gellan, a pioneer in this field of hypothermia.

"It is my conviction that hypothermia of 0 degrees centigrade is compatible with life of adult, large non-hibernating mammals if adequate perfusion of the vital organs is maintained However, as long as one was forced to rely on the hypothermic heart of the animal or patient to provide adequate perfusions, the procedure still encompassed the limitations of surface cooling. Only by making the circulation and oxygenation of blood independent of the haemodynamic changes of induced hypothermia has the barrier to the rate, degree and duration of cooling of large animals been removed During the last decade, the method of total body perfusion has been perfected to such a degree that problems today are not technical, but physiological in nature. Any of the available pump oxygenators can be adjusted to cool and rewarm the circulating blood."

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In his experience "The observed absence of a carbon dioxide and pH effect on the cardiac function of perfused dogs at low temperatures removes the importance of electrolyte changes from serious consideration." In addition, "of all the factors studied, adequate and constant perfusion of the vital organs with oxygenated blood is the 'conditio sine qua non' for survival of dogs after cooling ... and rewarming..... Except for a sufficient supply of oxygen to the cells at all times, all other factors are of secondary importance Thus all attempts to achieve a more fascinating and sophisticated explanation of the resuscitation of dogs from deep hypothermia by bringing in hormones, electrolytes, carbon dioxide and viscosity, have failed." All that is needed is a circulation to deliver oxygen to the tissues (Gollan, 1959).

How true these statements have been shown to be, not only by the work presented in this thesis, but also by recent reports in the literature (see Chapter II, Section C)! In addition, these statements hold true not only for dogs, but also for human patients subjected to cardiac surgery.

When the work discussed in this thesis was commenced, direct surgical intervention in the heart was already a reality. Surface hypothermia, owing to the limited time available in the heart, could only be used for simple defects and was very time-consuming. In normothermic heart-lung bypasses, the more complex defects - especially those where the high flow rates used caused a large coronary and bronchial return to the heart - remained difficult, as did surgery of the aortic valve with the necessary coronary artery perfusion.

A combination of profound hypothermia with extracorporeal circulation appeared to be the technique of the future, and the limited literature in this field supported this contention at

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that time, as it was felt that "profound hypothermia in man may bring startling new advances in the treatment of heart disease" (Cooper, 1960), the studies presented in this thesis were undertaken.

SECTION B - THE TECHNIQUE.

After performing the early trial experiments using various methods of inducing profound hypothermia in association with the bubble oxygenator, an apparently satisfactory method was evolved by incorporating the Bennington heat exchange unit in the arterial line of the bubble oxygenator.

Another apparently feasible and suitable technique to induce profound hypothermia also appeared at this time. This was the use of autogenous oxygenation with cardiac bypass (Drew et al, 1959, a and b; Shields and Lewis, 1959). It was tested experimentally (Terblanche and Barnard, 1960) but the technique incorporating an artificial oxygenator appeared to be better, and the literature tended to confirm this feeling (see Chapter II, Section C).

Thus, a feasible technique of inducing profound hypothermia using the bubble oxygenator was ready for trial. It was evident that this surgical technique for improving the operative conditions in the heart might evoke response in other organs, which could be detrimental, and a sound knowledge of such concomitant responses seemed essential. Only if the beneficial effects could be shown to outweigh any dangerous responses would the use of this technique be justified. It was therefore not only necessary to study the technical aspects of the bypasses but also to study the part played by at least some of the variables in the overall long

term /....

term safety of the application of this technique. For this reason, additional studies were undertaken in the dogs and, when the technique was eventually applied to patients, studies were also undertaken in them.

The results of the experimental investigations and the subsequent clinical application indicated that the method is technically satisfactory.

SECTION C - SAFETY.

The technique has been shown to be safe. A good survival rate was demonstrated both in the dogs and in patients subjected to the procedure, and the deaths which occurred were unrelated to the application of profound hypothermia. Although its induction brings about multiple changes in the "milieu interieur" of dogs and of man, these changes are promptly reversed on rewarming, and the reversal is maintained immediately after the procedure. An example is seen in the gross alterations which take place in renal function and which are promptly reversed with rewarming.

The small requirement of the body for oxygen during profound hypothermia is more than adequately met by the continuous flow of oxygenated blood, and in those cases in which this requirement is greater than expected, sufficient oxygen is still available. Only a minimal metabolic upset occurs, and the slight metabolic acidosis present after the procedure is easily counteracted by the administration of a small amount of sodium bicarbonate during rewarming. A distinct safety margin is added to cardiopulmonary

bypass /....

bypass by the addition of profound hypothermia. In these circumstances, both dogs and man can survive without circulation for at least a limited period of time, and in the event of some mishap, the machine can be stopped while the trouble is attended to and rectified. Longer perfusions become safe. This is evidenced by the hypothermic dogs in which these prolonged perfusions are associated with a good survival, despite the well-known fact that normothermic dogs stand perfusion notoriously badly.

The low flow rates used in the patients are safe as the tissues are protected by hypothermia. During normothermic perfusions, however, such low flow rates are dangerous. This safety is demonstrated by the high venous oxygen saturation usually present during the procedure and by the good survival rate. In addition, during rewarming, when a higher demand for oxygen is present in the tissues, "high flow" rates are again employed.

Although ventricular fibrillation (one of the most dreaded hazards of surface induced hypothermia) occurs, it is no longer a danger but is an advantage and is easily reversed. In addition, this method of producing a quiet heart is safer than chemical arrest. Oxygen embolism is not a problem, despite the placing of the heat exchanger in the arterial line of the apparatus during rewarming without using a bubble trap. The final demonstration of its safety is the safe clinical application of this technique which has been described.

SECTION D - ADVANTAGES.

The technique discussed has many advantages. One of its major advantages is the safety described above. The additional

safety /....

safety margin present when profound hypothermia is added to a cardiopulmonary bypass is clearly demonstrated by the dog perfusion in which a technical hitch occurred with the bypass apparatus. Despite complete cessation of circulation for 26 minutes, while the apparatus was repaired, the dog is one of the long term survivors.

Another very important advantage is the fact that surgery is greatly facilitated by the quiet heart and relatively bloodless field produced, and, when required, the circulation can be completely switched off for a while, safely.

The system of heat exchange is very efficient and cooling and rewarming are rapid, when compared with surface cooling. Low temperatures are easily attained and the rapidity of cooling and rewarming is facilitated by the "high flow" rates used during these phases. In addition, the bubble oxygenator is shown to be efficient during profound hypothermia by the consistently high arterial oxygen levels present throughout the bypasses.

The ventricular fibrillation that ensues is an advantage, and not a disadvantage, as the quiet heart produced facilitates surgery.

Another major advantage is the temperature gradient produced during this method of blood stream cooling, and it constitutes the basis of the success of the technique. The organs with the richest blood supply, and hence with the greatest metabolic activity, are cooled the quickest. On rewarming these organs are supplied with an adequate flow of oxygenated blood.

The Cape Town clinic's confidence in the advantages of this technique is demonstrated by its early clinical application, and the confidence was borne out by the results.

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SECTION E - POSSIBLE DISADVANTAGES AND DANGERS.

A disturbing feature in both the dog experiments and in the clinical cases is the high haemolysis of red blood corpuscles which is observed. This is felt to be due to the bubble oxygenator itself and its extent is related to the length of time of bypass, usually in the relationship of 1 mg. of plasma haemoglobin present for each minute of bypass. As this high haemolysis does not appear to be present in the other reported series, it is possibly an indication that some other oxygenator should be used when inducing profound hypothermia. On the other hand, the bubble oxygenator has been shown to be highly efficient and useful, and, in the patients, the haemolysis has not endangered life. Its retention in the circuit might thus well be justified.

The significance of the proteinuria that occurs during rewarming is not quite clear, but the possibility of this being an indication of renal damage should be borne in mind. In the writer's opinion, however, proteinuria per se is not necessarily an indication of renal damage, and, as the other renal function studies performed returned to control values on rewarming, it is felt that hypothermia does not endanger the kidney.

Two of the first 25 patients developed oliguria postoperatively. The exact reason for this remains uncertain and may well be due to some factor unrelated to the profound hypothermia. However, the possibility that this might be a danger should not be ignored.

In the first dog experiment, it was demonstrated that too long a period of total cessation of circulation during profound hypothermia causes irreversible changes in the tissues. Thus, until a more definite indication is obtained of the safe length of circulatory occlusion at different temperatures, total cessation of circulation should only be employed when essential to facilitate

surgery.

In the patients, an increased incidence of postoperative bleeding was noted, but the significance of this is not yet clear. Although the length of time of perfusion is increased by the cooling and warming, this disadvantage can be lessened in importance by careful planning.

As it is felt that no major disadvantages have as yet been shown, the continued use of this technique is justified.

SECTION F - COMPARISON WITH THE AUTOGENOUS OXYGENATION TECHNIQUE.

The alternative to the technique for producing profound hypothermia described in this thesis is autogenous oxygenation. The latter has been briefly discussed and the question is: do the findings indicate that the use of the method incorporating an artificial oxygenator is preferable to the use of autogenous oxygenation?

One of the major advantages claimed for autogenous oxygenation is that the best oxygenator available (i.e. the patient's own lungs) is used. In the present study, however, the great efficiency of the bubble oxygenator is clearly shown.

It has been demonstrated that some metabolism occurs in the tissues even during profound hypothermia. The evidence for this is the presence of an arterio-venous oxygen difference, a high venous carbon dioxide content, and an arterio-venous carbon dioxide difference during profound hypothermia. The mild metabolic acidosis which is present after the procedure is further evidence. In some of the patients and dogs, more marked metabolism than expected occurred. These factors indicate that at least low flows of oxygenated blood are desirable during profound hypothermia. When the autogenous oxygenation technique is employed, however,

as a result of the multiple cannulations necessary, the circulation is usually stopped completely to facilitate surgery. The total cessation of circulation represents one of the major hazards of this method of producing profound hypothermia. Two further points demonstrated in the dog experiments also indicate that total cessation of circulation might be dangerous. The first is that the brain temperature may lag a little behind the mid-oesophageal at times, thereby indicating that cessation of circulation at fairly high temperatures might be a danger. The second point is that too prolonged a period of suspended circulation definitely produces irreversible changes in the tissues, and this is clearly shown by the first dog experiment. Despite the claims of workers such as Gordon, that they know the arbitrary times of safe occlusion (Gordon et al, 1960, a), much more work is necessary before a definite indication of the safe length of time of circulatory occlusion at different temperatures can be attained.

These points alone indicate that the technique described in this thesis, with the maintenance of at least low flow rates of oxygenated blood during surgery, is preferable to the autogenous oxygenation technique.

SECTION 6 - INDICATIONS FOR FUTURE RESEARCH.

There is no doubt that, by the introduction of profound hypothermia in a homeotherm, a new "milieu interieur" is produced. The variations that occur in the few parameters studied in this thesis are a strong indication for further investigation along similar lines by workers in many branches of science and medicine throughout the world. It is only in this way that an increase in the knowledge, and ultimately the complete safety of the application of the technique in man, will be attained.

Certain /....

Certain of the studies discussed merit particular mention, as the implications of the changes found are not yet certain. These include the progressive fall in blood pressure that occurs with cooling, and the alteration that takes place in the blood balance during the procedure. A similar detailed study of the haemodynamic changes is indicated to those that have been undertaken with normothermic bypass (Sanger et al, 1960). The fall in serum potassium and rise in serum glucose that takes place during the procedure will also only be fully understood in the future as a result of further investigation. It was also pointed out that the apparent rise in peripheral serum cortisol may be an indication of a new balance being struck by the body to counter the changes in the internal environment.

The variations that occur in renal function constitute a very interesting aspect of this study, and the proteinuria that ensues with active rewarming on bypass is an aspect that definitely requires further investigation. The apparent blockage by the cold of the enzyme systems responsible for active tubular transport in the kidneys promises to be the opening in a new field of research in renal physiology, and further study in this field is at present being undertaken.

More detailed investigations than are at present available on the length of time of safe application of circulatory occlusion are also indicated.

Lastly, a study of profound hypothermia induced exactly as described in this thesis is required, but with the use of another artificial oxygenator to determine if lessened blood destruction would occur.

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SECTION H - OTHER INTERESTING OBSERVATIONS.

The well-known slowing of body processes brought about by hypothermia is confirmed. An indication of this is the initial slowing of the heart rate and the subsequent slowing of ventricular fibrillation.

The low mid-oesophageal temperature is demonstrated to be a useful and sufficiently accurate guide to the vital organ temperature. An unpredictable and wide variation occurs in the rectal temperature, following one of two patterns as a rule. It is once again demonstrated to be a fallacious guide to vital organ temperature. Although the brain temperature may lag a little, it is shown to be fairly accurately indicated by the low mid-oesophageal temperature. The temperature in the non-vital organs tends to lag considerably behind the mid-oesophageal, and even behind the rectal temperature, and an "after drop" may occur after cooling is discontinued.

The changes that occur in renal function during normothermic bypass are demonstrated to be due to a fall in glomerular filtration rate in the presence of normally functioning renal tubules. A sharp contrast is seen in the changes that occur during bypass with profound hypothermia. A progressive paralysis of tubular function occurs. The initiation of hypothermia causes a transient increase in the glomerular filtration rate and urine volume. The subsequent fall and rise in these two parameters follow the blood pressure variations closely. Rewarming promptly reverses all these changes, and the reversal is maintained immediately after the procedure. No proteinuria is present during the induction and maintenance of profound hypothermia, but with rewarming, proteinuria immediately occurs.

A progressive drop in blood pressure occurs with cooling, despite a constant flow perfusion rate, and this drop is felt to be due to the interplay of many factors, the most important of which is an altered autonomic response. A shift of blood occurs into the dogs on cooling with "high flow" rates, and this is felt to be due to pooling of blood in certain tissues on account of the autonomic nervous system paralysis which ensues. At least some metabolism takes place in the tissues during profound hypothermia, with an unpredictably greater demand being present in some cases. The metabolism is markedly increased during rewarming and the possibility of this increase being due to pooling of blood in certain tissues is mentioned. The necessity for administering small doses of sodium bicarbonate during rewarming, to counteract the mild metabolic acidosis that occurs, is demonstrated. The changes in the venous pressure, and in the sodium and chloride levels in the plasma, are not significant, and no further investigations are felt to be necessary here.

The lengthy perfusions in the clinical cases are felt to be an indication of the complexity of the lesions tackled in this series. The rise that occurs in the serum glucose level with the induction of hypothermia is felt to indicate diminished utilization and storage, and the fall in potassium level is felt to be due to a shift of this ion into the body cells and not to a loss of potassium from the body. The rise that occurs in serum-cortisol is apparently due to an even greater reduction of the metabolic breakdown of this substance than the reduction of output.

SECTION I - CONCLUSION.

Thus, the technique of inducing profound hypothermia with extracorporeal circulation developed in the laboratory, has been shown to be a safe and useful aid in cardiac surgery, by its

successful /....

successful clinical application, subsequent to experimental observation. Although "the technique is as yet in its infancy" and "the number of patients subjected to deep hypothermia is small" (Cooper, 1960), it will no longer be "some years before we can safely steer between the first rush of pioneer enthusiasm and over-biased inhibitory conservatism" as the enthusiasm of the pioneers has been shown to be fully warranted. Thus a new and very promising era in cardiac surgery has established itself. Despite this, many unknown factors still remain to be clarified when man is rendered profoundly hypothermic, and the final proof of the safety of the application of the technique will come only when a detailed knowledge of the physiology of profound hypothermia is attained. This will be achieved by the collection of the results of the efforts of workers in many branches of science and medicine throughout the world.

S U M M A R Y.

In this thesis it has been attempted to show that profound hypothermia with extracorporeal circulation, using the bubble oxygenator, is a safe and useful aid for cardiac surgery.

In reviewing the literature, the historical aspects are mentioned first, then the advances made in the field of hypothermia in the last decade and, finally, the various recent aspects of profound hypothermia reported are discussed.

The work is divided into two sections. The first consists of the experimental investigations using dogs, and the second, the clinical application of the technique developed during the experiments.

The development in the laboratory of the technique of inducing profound hypothermia, using the bubble oxygenator, is described, and the material, apparatus and methods used, and the results obtained in the dog experiments, are discussed in detail. The temperature gradients that were present and the variations in renal and metabolic functions that occurred are described separately.

The initial clinical application of this technique to cardiac surgery is presented. Once again the material, apparatus and methods used, and the results obtained with patients, are discussed in detail. An investigation of the plasma cortisol, potassium and glucose levels during and after the procedure is described separately.

In the final section, a detailed summary of the significant findings and conclusions is presented. It is pointed out that the technique is technically satisfactory, is safe, has many advantages

and /

and is preferable to the autogenous oxygenation technique. Although there appear to be some disadvantages, it is shown that no major ones exist. In addition, the lines along which future research should proceed are indicated, and the additional interesting observations made during the course of the study are reported.

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I am /....

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