DEEP HYPOTHERMIA

AN EXPERIMENTAL STUDY ON DOGS

with

TOTAL CIRCULATORY ARREST AND EXSANGUINATION

A THESIS PRESENTED TO

THE UNIVERSITY OF GLASGOW

FOR THE DEGREE OF

M A S T E R O F S U R G E R Y

by

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FOREWORD

The object of the experimental study presented in this thesis, was to provide a bloodless field for major surgical procedures on the heart, the great vessels and possibly the brain. In the future, when the homograft reaction has been solved, the technique described would be of particular value in transplantation of the major organs. This technique employs deep hypothermia combined with complete circulatory arrest and exsanguination, to provide the bloodless field.

Induced hypothermia when first used in clinical practice in 1940, showed early promise. Reduction of the metabolic rate of the body and of essential organs, in particular the brain, would be compatible with substantial periods of circulatory arrest. The barrier of ventricular fibrillation, however, limited the degree of cooling and consequently the reduction of metabolism upon which the period of circulatory arrest is dependent.

Satisfactory techniques have been devised for cooling small animals to low temperatures but these methods are insufficiently developed for universal application to man. The development of the extra-corporeal pump oxygenator and the concept of its use as a cardiac bypass, have recently overcome the dangers of ventricular fibrillation in deep hypothermia. During the past year such methods have been employed in this

country and the U.S.A. for surgery on the open heart.

It is hoped that the methods developed in this experimental study will further extend the field of surgery, particularly in those conditions which even at the present day are considered inoperable.

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The advice of many colleagues at St. Mary's Hospital is also acknowledged; to Professor Albert Neuberger for advice on biochemical problems; to Professor W.S. Peart and Mr. F. Diggins for the serotonin estimations; to Dr. Nancy Marston for confirming the haematological findings. Also to the Royal College of Surgeons of England and Professor David Slome and his staff, for facilities at the Buckston-Browne Farm.

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CONTENTS

INTRODUCTION

Four series of experiments are described in Chapters III, IV, V and VI. For convenient reference the series are referred to by the chapter number, followed by the number of the experiment in that particular series. Thus V/3 refers to experiment No. 3 described in Chapter V.

To avoid over burdening the text with numerical data this is tabulated in the Appendix.

CHAPTER I

REVIEW OF LITERATURE

Robert Boyle published a series of essays in 1683 titled "New Experiments and Observations Touching Cold". In these he questioned the accuracy of tactile sensation in estimating the degree of coldness and also observed that frogs and fish could survive short periods of freezing, but it was not until the invention of the thermometer by Fahrenheit, in 1714, that biologists had a suitable means of recording temperature. John Hunter in 1766 immersed carp, dormice, a toad and a snail in freezing solution for prolonged periods but was unable to effect survival. James Currie, in 1798, investigated the cause of death from exposure after shipwreck. He immersed two human volunteers in water at 44°F. for periods up to 45 minutes and recorded a fall of 8°F. in oral temperature. Subsequent exposure to a fresh wind at 44°F. caused a further fall of 3°F. in oral temperature. He also noted that the pulse at the wrist became slow and feeble, but the heart beat on palpating the chest was strong. Spallanzani in 1803 reported the effects of temperatures of -24°C. on unicellular organisms, insects, fish, reptiles, birds and mammals, and also noted that super-cooling caused less damage to the animal cell than freezing. Walther (1862) cooled rabbits to 18°C., and observed that survival occurred only if they were artificially rewarmed. He also observed that artificial respiration would

encourage spontaneous rewarming, but that a period of 24 hours was necessary to raise the temperature from 18°C. to 39°C. Simpson and Herring (1905) showed that anaesthetised cats could survive cooling to rectal temperatures of 16°C. and that artificial rewarming was necessary for survival. They also observed that a state of cold narcosis existed below 24°C., when no further anaesthesia was required.

Subsequently there was little physiological or clinical interest in hypothermia until 1939 when Fay and Smith (1939, 1940, 1941) cooled patients to 74° - 90°F. in an attempt to produce remission of carcinomatosis. Rectal temperatures were used as an index, and low temperatures maintained for up to four days. This failed to produce remission in primary tumours or metastases, but it was soon recognised that this technique, by lowering metabolism of the brain and other essential organs, might permit circulatory arrest during open heart surgery.

In 1950 Bigelow, Callaghan and Hopps surface cooled 39 dogs to the region of 20°C. and excluded the heart from the circulation for 15 minutes. 19 dogs died during this period, 14 due to ventricular fibrillation; 20 were revived to normal temperature and of these 6 survived completely. In two further experiments the temperature was maintained at 20°C. until ventricular fibrillation occurred after periods of 17 and 20 hours at this

temperature. In a subsequent paper Bigelow, Lindsay and Greenwood (1950) noted that ventricular fibrillation occurred in the range of 16°C. to 22°C. in dogs, and that venesection and rewarming the animals converted the fibrillation to normal rhythm in 20 out of 28 experiments. A mean of 80 ml. of blood was removed on each occasion. In three experiments repeated venesection totalling three-quarters of the blood volume, failed to prevent eventual death from ventricular fibrillation.

Ventricular fibrillation was subsequently confirmed as the limiting factor with induced hypothermia in non-hibernating homeotherms. The temperature at which this event occurs varies considerably with the experimental technique and the site and method of temperature recording. Burton and Edholm (1955) quote 14°C. to 20°C. as the critical level in the adults of non-hibernating species. Deterling, Nelson, Bhonslay and Howland (1955) observed ventricular fibrillation in 40 per cent of dogs under barbiturate anaesthesia, at temperatures below 23°C. Spurr, Hutt and Horvath (1954) observed this complication in 33 per cent of dogs cooled between 20°C. and 26°C. for 4 hours. In the author's experience ventricular fibrillation occurred in animals at higher temperatures after major surgical exposures and prolonged periods of physiological recordings. For the dog this was in the region of 25°C. to 28°C. oesophageal

temperature; a pig was observed to fibrillate at 30.5°C. and rats at 18°C. to 22°C. These observations were made while studying peripheral blood flows in hypothermia (Kenyon and Cooper, 1957). In adult man an oesophageal temperature of 28°C. to 30°C. is now generally accepted as the lower limit of safety with hypothermia induced by simple cooling methods. The author has observed irreversible ventricular fibrillation in two patients cooled to oesophageal temperatures of 26.8°C. and 27.4°C. while undergoing aortic resections for high aortic thromboses.

The young of most species, including man, can safely withstand cooling to temperatures 3°C. to 5°C. lower than the adult before ventricular fibrillation supervenes. Adolph (1951) has shown that this infantile tolerance to hypothermia is lost at an early age in cats, rabbits, guinea-pigs and rats.

Certain small mammals, which include the hedgehog, hamster, marmot, dormouse, ground squirrel and the bat, enter a stage of deep hibernation when faced with winter, or an artificial cold environment. The deep body temperature approximates to 1°C. higher than that of the environment, but when the latter approaches freezing point, the animal re-awakes (Spallanzani, 1803; Simpson and Herring, 1905; Johnson, 1931). Lyman (1948) showed that the cheek pouch and rectal temperatures of the golden hamster were 1°C. above that of their environment at 5°C. but when this

was lowered to 0°C. the majority re-awakened and rewarmed spontaneously, a few remained in deep hibernation without furtherfall of temperature and a small proportion continued to cool and failed to recover. During this period of deep hibernation the heart continues to beat at a much reduced rate, and the respiration rate is considerably diminished, but there is no cessation of the circulation. The metabolism is 1/30 to 1/100 of normal and Benedict and Lee (1938) observed a respiratory quotient close to 0.7, indicating that fat metabolism is almost exclusively the source of energy.

In 1951 Andjus showed that a small proportion of rats cooled to a body temperature of 0°C. to 2°C. could be re-animated after a cardiac and respiratory standstill of 40 to 50 minutes. This most interesting observation was followed up by a classic series of cooling experiments on mice, rats, golden hamsters and monkeys at the Medical Research Council Laboratories in London. Doctors A.S. Parkes, A.U. Smith, R.K. Andjus, J.E. Lovelock and S.A. Goldzveig (1955, 1956, 1957) developed a technique for cooling and super-cooling these animals with a high proportion of survivals. The experimental animals were placed in Kilner jars in an atmosphere of carbon dioxide and the ambient temperature reduced to 15° - 20°C. The combined effects of hypercapnia, hypoxia and cold produced a state of cold narcosis and when the

colonic temperature was reduced to 15° - 20°C. they were then immersed in ice cold water and covered with crushed ice. The colonic temperatures fell rapidly and when in the region of 5°C. the animals were transferred to fluid baths at -3°C. to -5°C. Respirations ceased at approximately 4°C. and heart action between 1°C. and 2.5°C. When colonic temperatures reached -0.5°C. to -1°C. one of three events occurred: (i) the animals became frozen with formation of ice crystals in the tissues, and without further fall of temperature; (ii) the animal super-cooled with a further fall in temperature to -3°C. to -5°C. then spontaneously formed ice crystals with a sudden rise of temperature to 0°C.; (iii) super-cooling was maintained until re-animation commenced. Rewarming by microwave diathermy proved the most successful of several methods tried. This was assisted by gentle artificial respiration when the colonic temperature reached 10°C. Pre-ingestion by the animal of 20 per cent propylene glycol was found to favour super-cooling, and Dr. Audrey Smith stated "the results strongly supported the previous suggestion that animals pre-fed with an adequate amount of propylene glycol had an increased tendency to super-cool. They showed that super-cooling was greater among propylene glycol drinkers immersed in fluid at -5°C. with body temperatures at +5°C. than those initially warmer or cooler". Using these methods 90 per cent of golden hamsters

were super-cooled to deep colonic temperatures of -3°C. to -5°C. and were successfully revived after periods of 50 to 70 minutes of complete circulatory arrest, with a high proportion of survivors. A high proportion of super-cooled rats survived (Andjus, 1955) but monkeys were less satisfactory (Smith, 1957).

Niazi and Lewis (1954, 1956, 1957) developed a similar technique in which rats, dogs and monkeys were cooled to near 0°C. with subsequent recovery. The animals were surface cooled and breathing assisted with a respiratory apparatus. Rewarming technique involved the application of warm packs to the chest until cardiac action re-commenced and the body was then warmed to 40°C. With this method it was possible to survive 24 out of 47 rats from -4°C. to 8.5°C., 10 out of 20 dogs from 0°C. to 11.5°C., and 5 out of 6 Java monkeys from 4°C. to 9°C. Niazi and Lewis (1958) indeed cooled an adult female patient to a rectal temperature of 9°C. in an attempt to obtain remission of a carcinoma of ovary. The heart was arrested for 60 minutes before rewarming and the patient subsequently lived for 38 days. Post mortem examination showed that there had been no remission of the primary carcinoma or its metastases. These techniques of cooling and super-cooling to low temperatures, although successful in small animals, have not proved satisfactory for general application in larger animals or man. Ventricular fibrillation was the main barrier and much

physiological observation and experimental endeavour failed to solve the problem of the mechanism.

Experimental studies on plasma electrolytes have produced many variables depending upon the nutritional state of the animal, methods of anaesthesia and pulmonary ventilation, and the experimental production of cardiac arrest. Most authors are agreed that there is no significant change in the plasma sodium values. Fleming (1954), Deterling, Nelson, Bhonslay and Howland (1955), and Da Costa, Ratcliffe and Gerbode (1954) recorded normal values for plasma potassium. Bigelow, Lindsay and Greenwood (1950) noted elevation of potassium in the dog with circulatory arrest, and Elliot and Crismon (1947) a less marked elevation in rats, due to liver glycogenolysis. McMillan, Melrose, Churchill-Davidson and Lynn (1955) demonstrated a reduction of potassium to 85 per cent of normal with moderate pulmonary hyper-ventilation, and Swan, Zeavin, Holmes and Montgomery (1953) a reduction to 70 per cent with hyper-ventilation of the lungs. Gollan, Olsen and Rudolph (1956) demonstrated a loss of intra-cellular potassium in both resting skeletal muscle and beating cardiac muscle in the dog at 19°C., this reduction being significantly greater in the active heart muscle. Calcium was slightly elevated in the rat at 25°C. in Elliot and Crismon's experiments (1947), and also in the dog at 19°C. in McMillan, Churchill-Davidson and Lynn's experiments (1955).

Magnesium was normal as recorded by Fleming (1954) and McMillan, Melrose, Churchill-Davidson and Lynn (1955).

The arterial pH in the dog, cooled and breathing spontaneously, shows an initial rise while shivering; this is followed by a progressive fall. Brown and Miller (1952) demonstrated ventricular fibrillation in dogs by sudden increases in pCO_2 of arterial blood and Swan, Virtue, Blount and Kircher (1955) produced alkalosis by pulmonary over-ventilation and reduced the incidence of ventricular fibrillation in hypothermic dogs. Osborn (1953) prevented ventricular fibrillation in dogs cooled to a rectal temperature below 19°C. by maintaining a high serum bicarbonate. However these methods did not prevent ventricular fibrillation at lower temperatures. Covino and Hegnauer (1955) even demonstrated that ventricular fibrillation could be produced at normal temperatures by sufficient alternation in the pH of arterial blood. Cahn, Melon and Dubrasquet (1953) claimed a reduction of the incidence of ventricular fibrillation by sino-auricular node blocade with local anaesthesia, as also did Riberi, Siderys and Shumacker (1956). Montgomery, Prevedal and Swan (1954) tried the effect of systemic prostigmine but these methods only reduced the temperature at which fibrillation occurred by a few degrees centigrade.

In the majority of clinical and experimental studies on

hypothermia the body temperature has been reduced by surface cooling. In 1951 Laborit and Huguenard reported the use of a "lytic cocktail" consisting of chlorpromazine, largactil and pethidine, which, by lowering the metabolic rate of the body, produced a state of "artificial hibernation". This method was extensively used by the French Army for the treatment of battle casualties in the latter part of the Indo-China War of 1946-1954, and although of apparent value in this respect, when used under controlled conditions, the "lytic cocktail" does not effectively reduce deep body temperature.

In 1952 Delorme investigated a method of blood stream cooling by diverting the peripheral arterial flow through a cooling coil. Cooling was rapidly produced at the rate of 0.5°C. per minute. Brock and Ross (1955) developed a method of veno-venous blood stream cooling. Blood is removed from the superior vena cava, pumped through a plastic coil in contact with refrigerant at -4°C. and returned to the inferior vena cava. Rewarming is accomplished by raising the temperature in the heat exchanger to 44°C. This has proved a rapid and efficient method of producing hypothermia of 28°C. to 30°C. in patients undergoing cardiac surgery and 200 patients have been cooled and rewarmed by this method (Ross, 1959).

Gollan, Blos and Schuman in 1952 reported the experimental use of a simple pump oxygenator in which hypothermia to 30°C. was

used with the object of reducing extra-corporeal bypass flow during cardiac surgery. This method was developed, and in 1954 Gollan, Hamilton and Meneely reported the survival of 13 out of 17 dogs cooled below 10°C. Subsequently Gollan, Grace, Schell, Tysinger and Feaster (1955) recorded 9 survivors out of 14 dogs undergoing cardiotomy at temperatures between 4°C. and 6°C. The animals were pre-cooled by surface methods to 30°C. The femoral veins were cannulated, one cannula lying in the right atrium and the second in the inferior vena cava. Venous blood was syphoned to a bubble oxygenator and then pumped through a metal coil immersed in brine solution and returned to a catheter in the femoral artery, the tip of which was introduced to lie in the brachio-cephalic artery. This method produced a partially selective cooling of the upper half of the animal, the oesophageal and rectal temperatures being 4°C. and 22°C. respectively in a typical experiment. Ventricular fibrillation was no problem with this technique, cardiac arrest occurring at 13°C. on cooling and normal cardiac contraction recommencing at approximately the same temperature on rewarming.

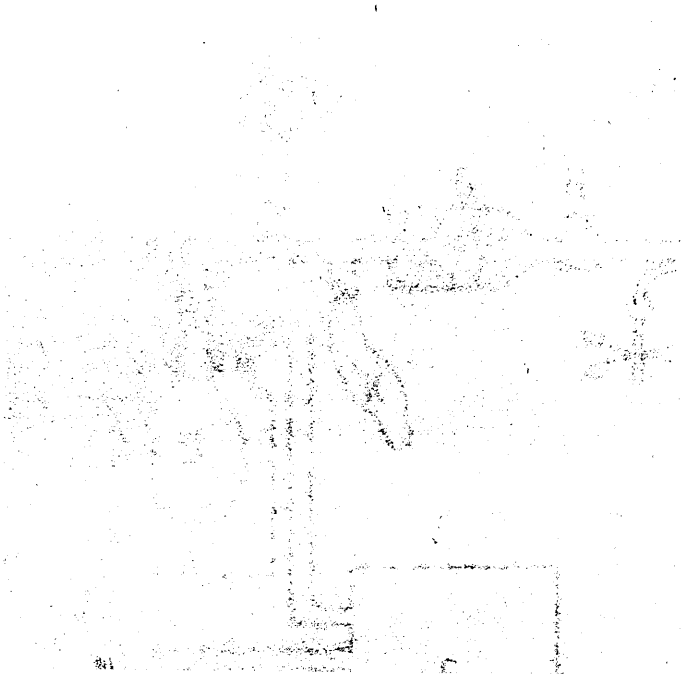
Juvenelle, Lind and Wegelius (1954) surface cooled dogs by immersion in ice water to the point of ventricular fibrillation then used a pump oxygenator to control the fibrillation. 10 out of 44 dogs recovered from rectal temperatures of 9°C. to 19°C. Senning (1954) also used a pump oxygenator to cool 12 dogs to

14°C. to 20°C. but noted that "ventricular fibrillation appeared at the least touch" at low temperatures. In 1957 Kenyon and Ludbrook reported a method of total body cooling in dogs to temperatures of 4.7°C. to 7°C., with cardiac recovery in each of six experiments. In 1958 Kirklin, and Sealy, Brown and Young, used a similar method to cool patients to 20° - 30°C. while undergoing open heart operations. Sealy, Brown, Young, Smith and Lesage (1959) subsequently recorded their experience using hypothermia in 88 patients undergoing open heart surgery. In seven patients the oesophageal temperature was reduced to 9° - 20°C. and three deaths occurred in this group.

Drew, Keen and Benazon (1959) described a most interesting technique for reducing temperatures to 10° - 15°C. with extra-corporeal circulation and heat exchanger, but without an oxygenator. The left ventricle is bypassed through a pump and heat exchanger, the right ventricle maintaining a pulmonary circulation. When this reaches the point of failure it is bypassed by a second pump which is continued until the oesophageal temperature reaches 10°C. to 25°C. and both pumps are then discontinued for periods of 30 to 45 minutes. Rewarming is accomplished by reversing the procedure. Initial experiments on dogs were not attended by survival, but Drew and Anderson (1959) reported five recoveries in seven patients undergoing heart surgery

at 15°C. by this method.

In 1959 Kenyon, Ludbrook, Downs, Tait, Brooks and Pryczkowski reported an experimental study on dogs which were cooled to temperatures of 5°C. or below, exsanguinated and maintained for periods of 30 to 45 minutes without circulation. On subsequent rewarming there were eight survivors out of ten final consecutive experiments.



CHAPTER II

APPARATUS AND METHODS

ANAESTHETIC APPARATUS

In the acute series of experiments, anaesthesia was maintained with a Palmer-Starling respiration pump. The suction and pressure cylinders were connected to a Y piece and expiratory valve, then to a cuffed endotracheal tube. Air was used as the respiratory gas and polyvinyl chloride tube for the connections.

For the survival experiments this apparatus was extensively modified as shown in Figure 1.

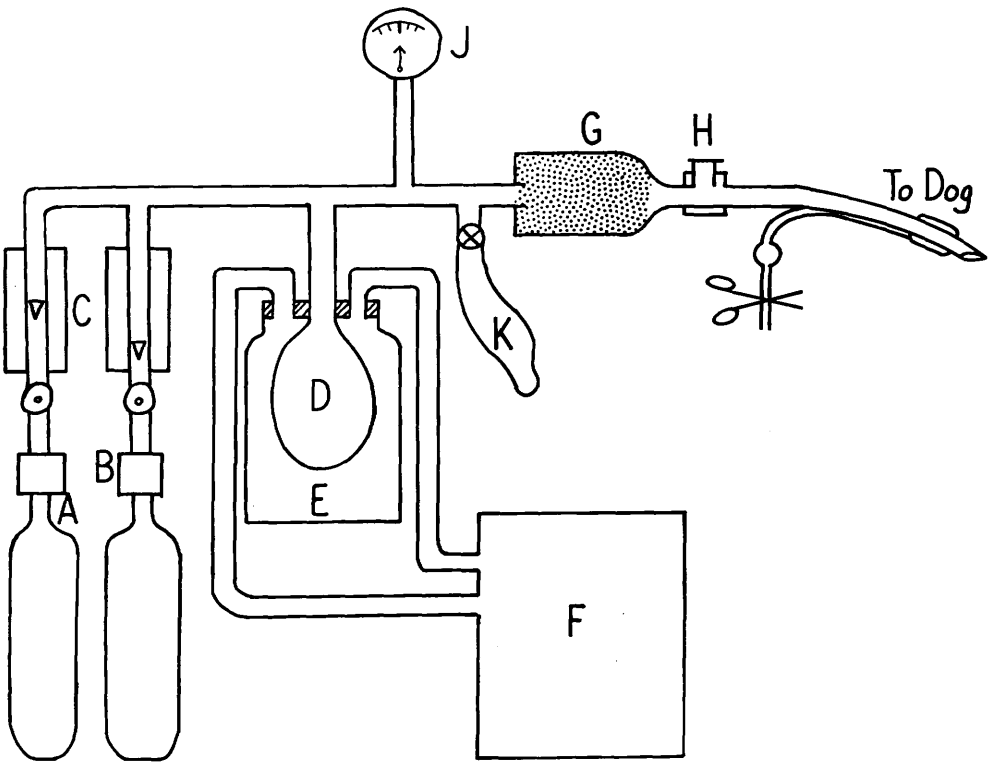


Figure 1. Diagram of Anaesthetic Apparatus.

Nitrous oxide and oxygen cylinders (A) with reducing valves and gauges (B) were connected to twin-flow meters (C). A side arm led to a rubber bag (D) enclosed in an airtight jar (E). The bag was alternately inflated and deflated by Starling-Palmer pump (F). Anaesthetic gas mixture was transmitted to a Water's Canister containing calcium chloride (G) thence via an expiratory valve (H) to the cuffed endo-tracheal tube. A positive and negative pressure gauge (J) calibrated $\pm$35 cm. water was subsequently fitted to avoid over inflation of the lungs, and an additional rubber bag (K), also fitted for hand inflation of the lungs if required. When the latter was not in use the valve was closed.

PUMP OXYGENATOR

A Melrose type pump oxygenator, designed and constructed by the author, was used. The oxygenator design closely follows the description given by Melrose and Aird (1953). A small oxygenator of approximately 0.5 sq. meter surface area, as illustrated in Figures 2 and 3, was used for acute experiments. This was subsequently enlarged by 50 per cent and fitted with an improved collecting chamber. After assembly the oxygenator was rinsed with a solution of 1 gm. of Antifoam A dissolved in 10 ml. of ether.

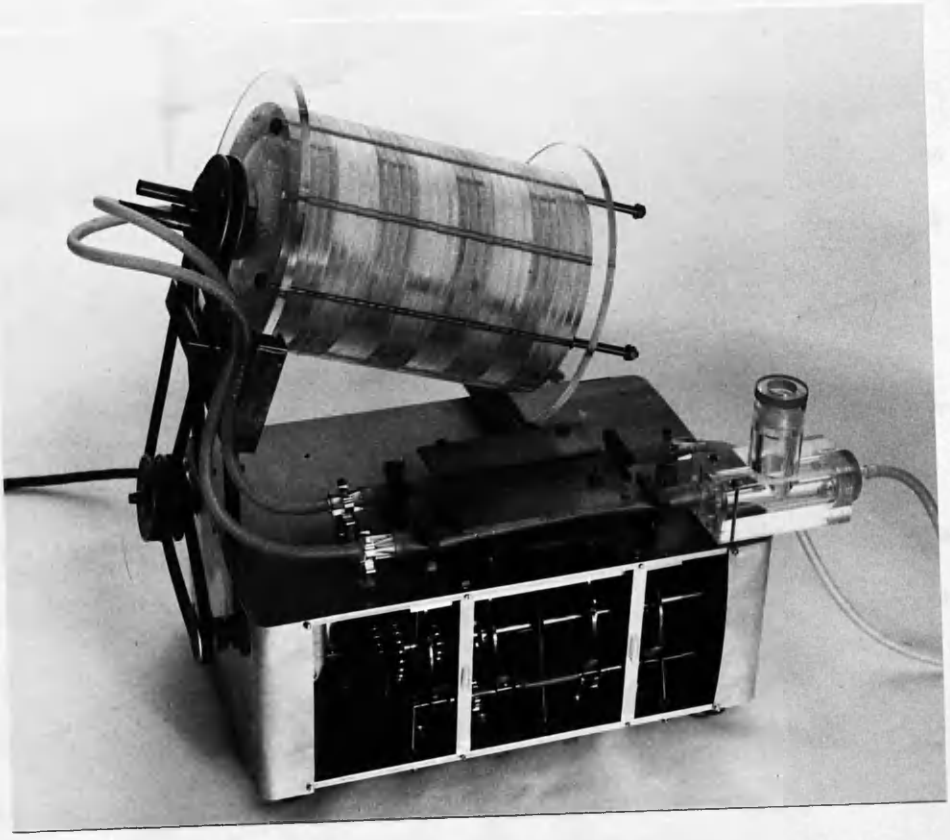


Figure 2. The Pump Oxygenator

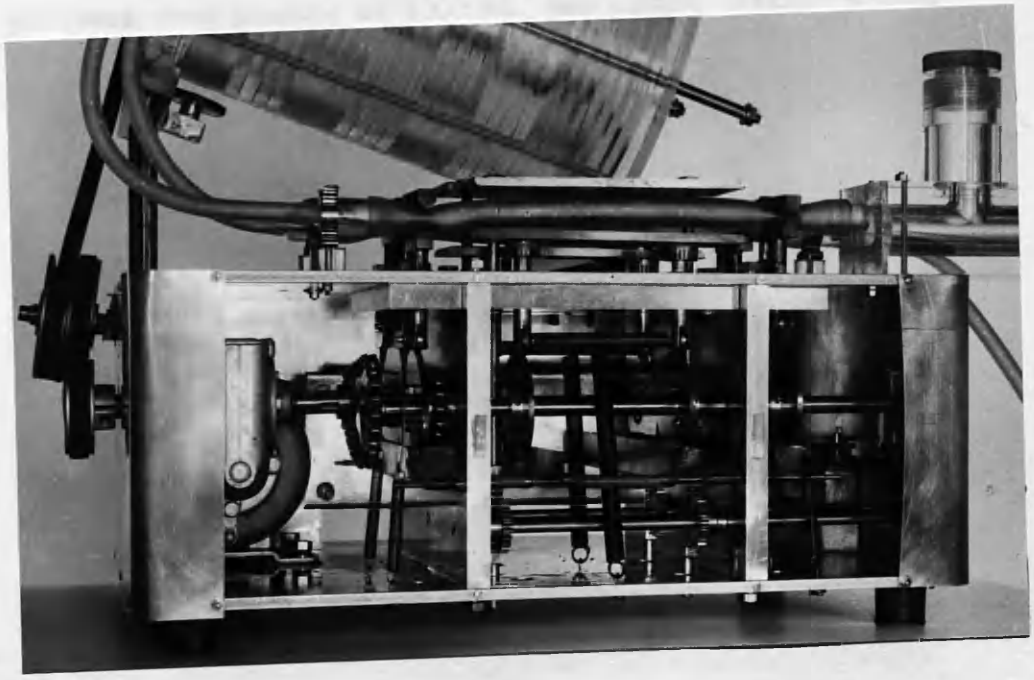


Figure 3. The Pump Oxygenator Mechanism.

An atmosphere of 95 per cent oxygen, 5 per cent carbon dioxide was maintained within the oxygenator by a flow of 4 litres per minute in acute and early survival experiments. In later survival experiments 97 per cent oxygen, 3 per cent carbon dioxide at 8 litres per minute were supplied to the oxygenator. Particular attention was paid to the design and timing of the cams which actuated the twin pumps. The events were calculated from normal human E.C.G. traces and data obtained from Lewis and Wiggers and quoted by Samson Wright (1952). It is important to avoid excessive pressure within the compressed tubes after closure of the inlet valve and prior to opening of the outlet valve. The pump described does not exceed 200 mm. Hg. internal pressure when pumping at 1000 ml. per minute against a mean resistance of 100 mm. Hg.

As illustrated in Figures 2 and 3, both suction and pressure lines are connected, but in practice a gravity drain of 15 cm. from the left atrium to the oxygenator was found to be more satisfactory than the use of the suction pump.

HEAT EXCHANGERS

Three different types were used. A 9 metre coil of tygon tube 4.8 mm. internal diameter and 1.6 mm. wall thickness was used for the acute experiments. This was immersed in a mixture of brine and ice during cooling, and for rewarming a water

temperature commencing at 15°C. gradually increasing to 40°C. was used. The second type (Mark I) consisted of two 9-way stainless steel connections with 9 metre lengths of 2.5 mm. bore x 1 mm. wall, polyvinyl chloride tubing interconnecting. This was arranged in a spiral and contained in a cylinder (Figure 4).

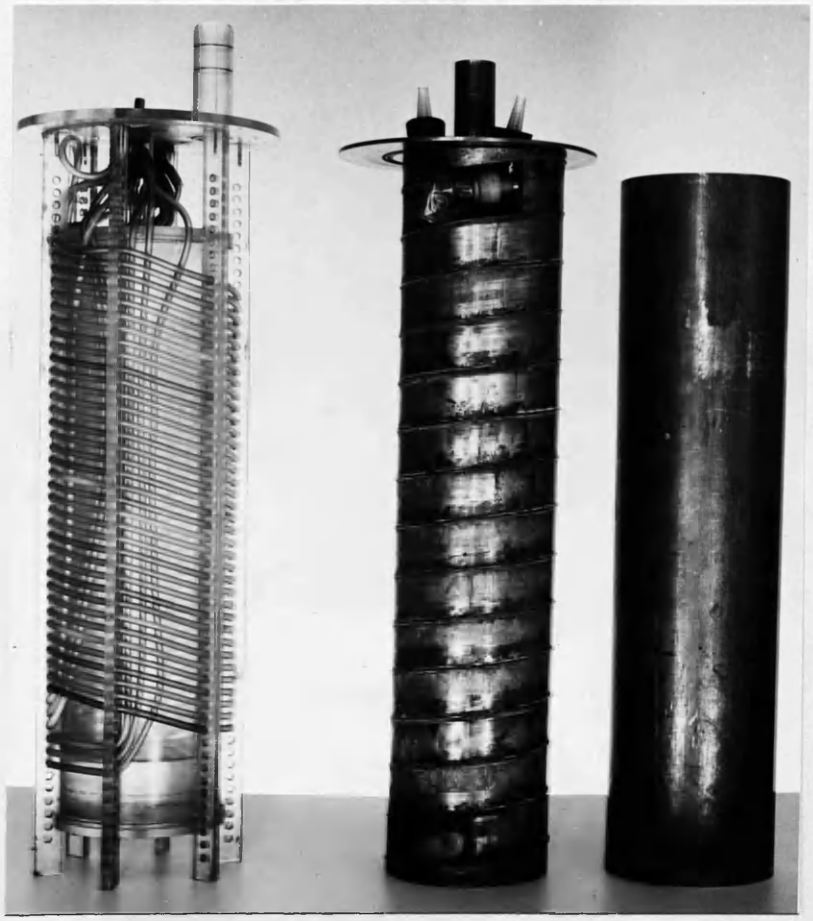


Figure 4. The Heat Exchangers. Left Mark I.
Centre Mark II, with outer casing on right.

The iced brine coolant or rewarming fluids were circulated through the cylinder with a Stuart No. 12 centrifugal pump at the rate of 500 gallons per hour. This heat exchanger was used in the early survival experiments.

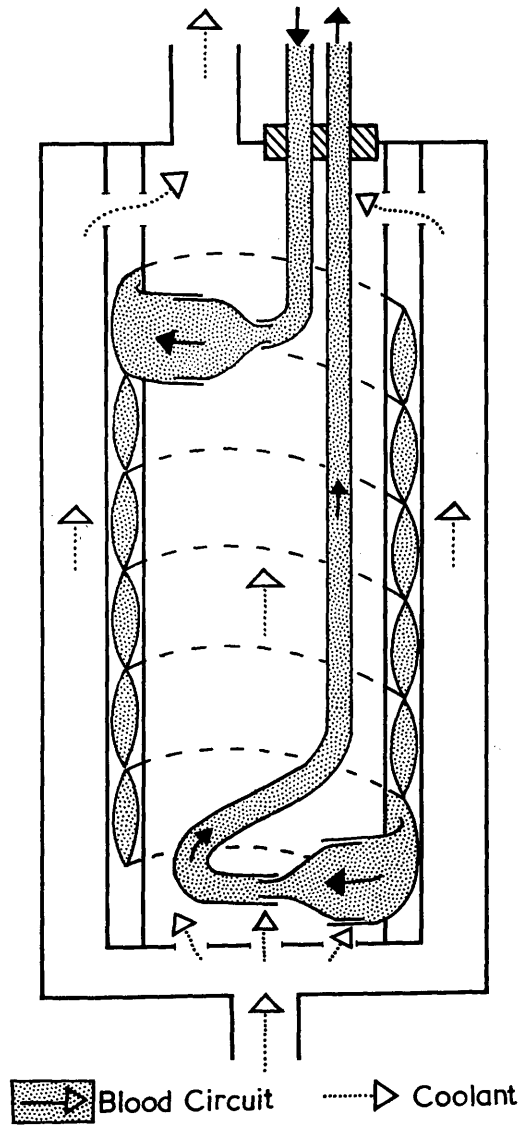


Figure 5. Diagram of Mark II Heat Exchanger Circuits.

The third heat exchanger (Mark II), shown in Figures 4 and 5, consisted of a 2 metre length of layflat nylon tube 25 mm. wide and 0.1 mm. wall thickness, wound spirally on a copper cylinder 10.2 cm. outside diameter, and located by a 1.5 mm. diameter copper wire soldered in a spiral to the cylinder. An outer cylindrical sleeve of 10.8 cm. internal diameter limited the cross section of the layflat tube to 3 mm. and provided ridged support. At each end a nylon adaptor connected the layflat tube to the circuit tubes. This unit was enclosed in a perspex container through which refrigerant was pumped at the rate of 500 gallons per hour. Comparative efficiency between type 2 (Mark I) and type 3 (Mark II) is illustrated in Figure 6.

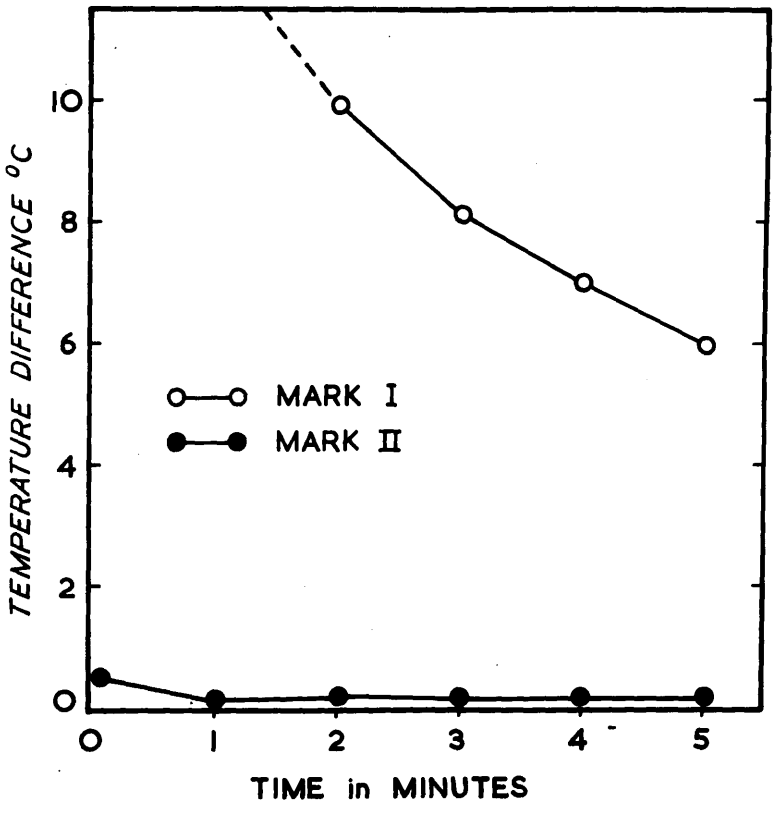


Figure 6. Comparative Efficiency Curves of Mark I and Mark II Heat Exchangers.

Dextran at a constant temperature of 37°C. was pumped through the heat exchanger at a rate of 500 ml. per minute. Refrigerant at 14°C. was circulated at 500 gallons per hour. The temperature difference between the outflow of dextran and the refrigerant was noted, and recorded against the time from commencing the circulation. The temperature difference for the Mark II heat exchanger was at all times within 0.5°C. of that of the refrigerant, and this obtained for flows up to 1000 ml. per minute. Resistance was also low, a pressure drop of 20 mm. Hg. across the heat exchanger occurred with a blood flow rate of 500 ml. per minute at an inflow pressure of 120 - 140 mm. Hg. This heat exchanger was used in all the later survival experiments.

TEMPERATURE RECORDING

Copper-constantan thermocouples of 32 SWG were enclosed in thin nylon tube of 1.5 mm. outside diameter. Specially wound series resistances were incorporated in order that each had a constant total resistance. Six thermocouples were connected to a 6 way copper to copper selector switch, thence to a Pye Scalamp galvanometer, calibrated to give a direct temperature recording from 0°C. to 40°C. Melting ice stirred in a vacuum flask was used for the reference junction. This apparatus responded to temperature changes within three seconds and was accurate to within $\pm$0.2°C. In a few early experiments, mercury glass

thermometers, calibrated in 1/10ths of degrees were used for temperature recording.

ARTERIAL AND VENOUS PRESSURE RECORDING

Arterial and venous pressures were recorded by mercury and water manometers respectively. These recorded directly in ink on graph paper attached to a revolving drum. Particular attention was paid to setting the zero point of both manometers at the level of the left atrium. Side connections near the cannulae provided for arterial and venous blood sampling, and also for intravenous medication and fluid replacement.

E.C.G. Standard lead electrocardiograms were recorded in the majority of experiments with a direct writing Elema Mimograph electrocardiogram.

E.E.G. was observed in six experiments on an apparatus constructed and loaned by F. Watson, Esq. Waves were observed on an oscilloscope and records obtained by photographing these with a reflex camera.

HAEMATOLOGY

Haematocrits and Plasma Haemoglobin. Arterial blood was spun in a centrifuge, and the haematocrits noted. Supernatant plasma was estimated for haemoglobin concentration in a Unicam SP.500 spectrophotometer.

Blood Coagulation Times were estimated by the method of

Lee and White (1913).

White Blood Cells and Platelets. Films of fresh blood were made on a microscope slide, fixed by heat and stained with haematoxylin and eosin. These were then examined under a microscope and the findings confirmed by an experienced haematologist.

Plasma Fibrinogen was measured by the method of Kekwick and Mackay (1954).

BLOOD CHEMISTRY

Arterial pH was measured by the method described by Wynn and Ludbrook (1957) with a E.I.L. pH meter at 38°C.

Sodium and Potassium were estimated from plasma samples in an E.E.L. flame photometer.

pCO_2 and tCO_2. Plasma bicarbonate was measured by the manometric method of Van Slyke. The pCO_2 was calculated from this result and the arterial pH, by a nomogram based on the Henderson - Hasselbalch equation.

Total Plasma Serotonin was estimated by the spectrofluorometric method for whole blood, described by Udenfriend, Weissbach and Clark (1955).

Serum Osmolarity. This was measured by an osmometer, the depression of the freezing point indicating the osmolarity.

EXPERIMENTAL PROCEDURE

Two basic types of experiments were performed and the preparation for each varied:

(1) Acute Experiments.

(2) Survival Experiments.

A few of the acute experiments were performed with the identical preparation for survival experiments, with the purpose of obtaining controlled physiological data.

ACUTE EXPERIMENTS

Unselected mongrel dogs were used weighing 10 - 17 kg. Anaesthesia was induced with intravenous sodium thiopentone, the trachea intubated and pulmonary ventilation maintained with the respiration pump. The chest, abdomen and inguinal regions were shaved and a femoral artery and vein exposed. The vein was cannulated and a fluid drip of 0.9 per cent sodium chloride commenced. Additional sodium thiopentone was given as required through the drip tubing. The chest was opened through a transverse incision in the 3rd interspace and the sternum split transversely, after ligation and division of the internal mammary vessels. Meticulous haemostasis by diathermy coagulation of bleeding points was observed during the dissection. The subclavian artery on the left side was isolated with a tape, and the pericardium incised to expose the right atrium. The

vena azygos was ligated. The pump oxygenator, heat exchanger and bubble trap were primed with 750 ml. of dextran, [Dextravan-(Benger)6% in 0.9% saline] and pumped on a closed circuit to eliminate all bubbles. Heparin, the dosage of which varied between 5 mg. and 10 mg. per kilogram body weight, was administered intravenously to the experimental animal and the femoral artery cannulated and connected to the pressure recorder. A curved cannula was then inserted in the subclavian artery to lie with its orifice in the aortic arch, the distal end of the artery having been ligated. Venous catheters were inserted through separate incisions in the atrial appendage, to lie in both inferior and superior venae cavae. The stab incisions were closed with previously inserted purse string sutures. This completed the extra-corporeal perfusion circuit shown in Figure 7.

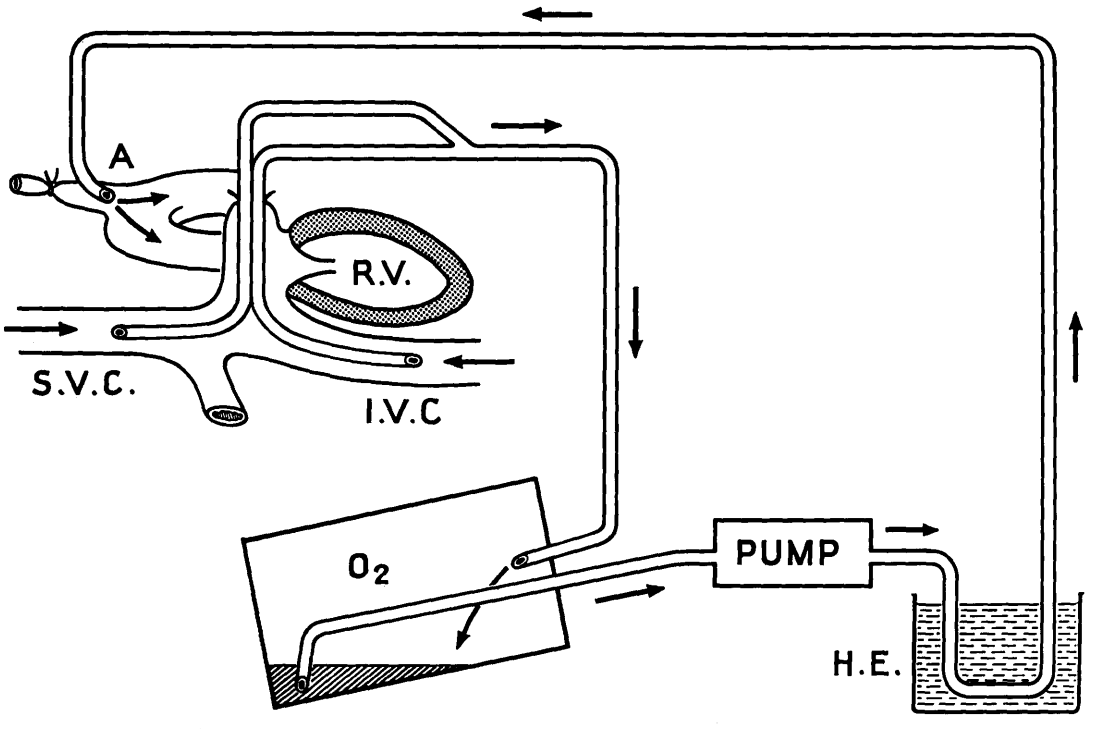


Figure 7. Extra-Corporeal Perfusion Circuit.
R.V. = right ventricle. O_2 = oxygenator.
H.E. = heat exchanger. A ≅ aorta.

A clamp on the venous tube was then gradually opened permitting blood from the cavae to syphon to the oxygenator through a fall of 15 cm. The bypass was closed and the pump output increased to balance the inflow with the venous outflow. Arterial and

venous pressures were observed at this stage, although the venous pressure proved unreliable in the relatively small animals, frequently running at -7cm. to - 12 cm. of water and was therefore not always used. When the cardio-pulmonary bypass was stabilised the temperature of the heat exchanger was reduced to 0°C. to -1°C., and the extra-corporeal circulation continued until the desired deep body temperature was reached. The animal was then either rewarmed immediately, or the extra-corporeal circulation was discontinued for a given period, after which rewarming commenced. The rewarming was accomplished by raising the temperature in the heat exchanger by varying stages, and when completed the extra-corporeal circulation was discontinued and the venous and arterial catheters clamped and removed. The dogs were then observed for short periods, and sacrificed before recovering consciousness.

SURVIVAL EXPERIMENTS

Similar dogs were used, but it was found advantageous to observe the animal for a few days before the experiment, when it could have an adequate diet and vitamin intake. 150 mg. of Aureomycin were given orally on each of the two days preceding, and in later experiments 0.125 mg. of digoxin was given on the day before and the morning of the experiment. Donor blood was collected on the same day. 1000 ml. contained 40 mg. heparin to prime the apparatus and 1000 ml. with 120 ml. 3.8 per cent

buffered acid citrate dextrose solution for post-operative replacement.

The heat resisting parts of the apparatus, which included catheters, circuit tubing and bubble traps, were sterilised in an autoclave at 121°C. and 15 lb. per square inch pressure for 30 minutes; non-resistant parts, which included the oxygenator and heat exchanger, were sterilised over 24 hours with an antibiotic solution of 2 million units of penicillin and 1 gramme of streptomycin to the litre of saline. A no-touch technique was observed while assembling the apparatus, and full surgical aseptic precautions were taken during the operative procedures.

The dog was premedicated with 1/200 gr. atrophine sulphate, anaesthesia induced with intravenous sodium thiopentone through a foreleg vein and maintained with additional dosage of either this drug or pethidine. The trachea was intubated and pulmonary ventilation maintained with a 50 : 50 nitrous oxide, oxygen mixture, on the respiration apparatus described above. Chest, abdomen and groins were shaved, prepared with iodine and the operative field excluded with sterile towels. In experiments III/1 to IV/2 a thoracotomy was performed as described above, but this resulted in wound sepsis in survivors 1 and 2, and the first control experiment. Subsequently for experiments IV/3 to VI/6 the exposure described by Andreason and Watson (1953) was

adopted. This involves raising a ventral flap of chest wall before performing the 3rd interspace thoracotomy and is illustrated in Figures 8 and 9.

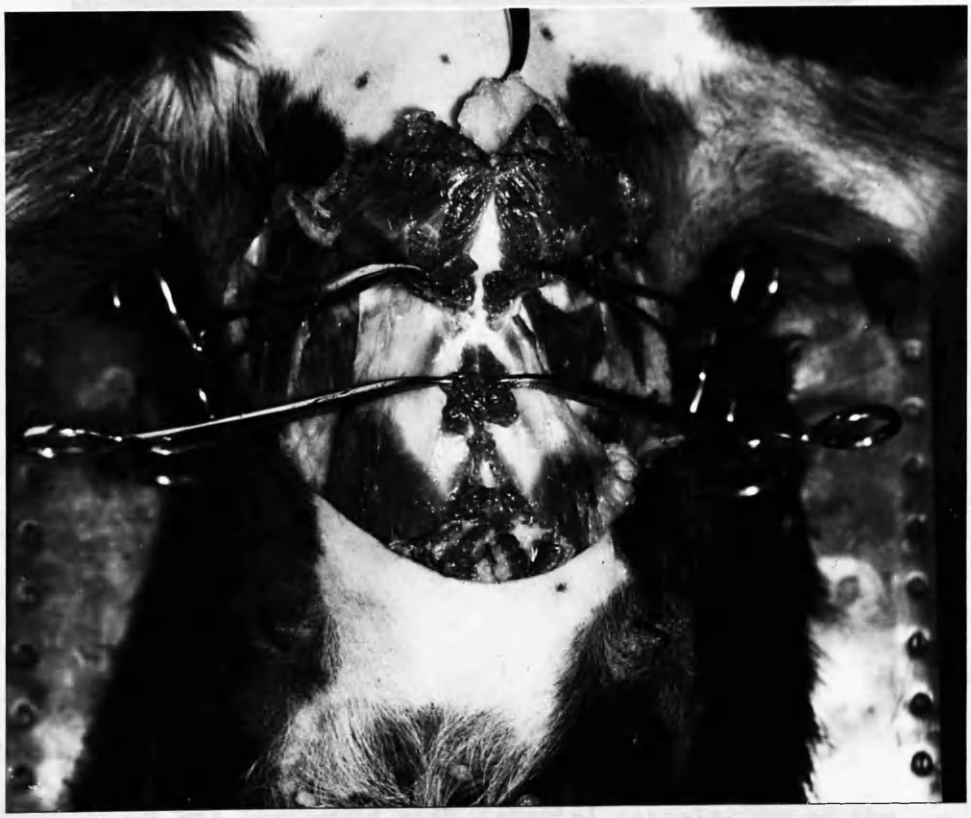


Figure 8. Exposure.

Figure 9. Closure.

In the final group of survival experiments a right 4th space thoracotomy was performed with arterial cannulation of the external iliac artery through an oblique muscle splitting incision in the lower abdomen. This method was first used in experiment VI/7 and all experiments thereafter. Different methods of cannulating the venae cavae were tried but the double incision

sealed by purse string sutures proved the most satisfactory.

Thermocouples were routinely placed in the porta hepatis through an epigastric incision and per rectum to lie in the lower colon, 10 cm. from the anus. Particular attention was paid to their accurate location.

When the surgical exposure was nearing completion, the extra-corporeal pump oxygenator was assembled and irrigated with normal saline solution. The apparatus was then primed with heparinised donor blood which was slowly pumped and oxygenated, through a closed circuit. 5 or 10 mg. heparin per kilogram body weight was administered intravenously to the experimental animal and the femoral artery cannulated to record blood pressure. The left subclavian artery or the iliac artery was then cannulated, and in the latter case the tip placed in the mid portion of the abdominal aorta. The cannula was connected to the pump oxygenator and bubbles carefully removed through a side tube. The venae cavae were cannulated as previously described, connected to the venous line via a Y piece, and bubbles removed through a side tube. The general method of cooling and rewarming followed that described for the acute experiments, with some minor modifications which will be described subsequently.

When rewarming was complete, the venous cannulae were

removed first and the atrial appendage securely ligated. The pericardium was closed with interrupted silk sutures and a ventral drain inserted through a separate stab wound to lie antero-lateral to the pericardium. A calculated dose of protamine sulphate was then given, the iliac catheter removed and the vessel doubly ligated. The abdominal wound was then closed in layers, the porta hepatis thermocouple removed and the wound closed. All blood was now sucked from the chest and the ribs approximated with interrupted braided nylon sutures. Continuous silk sutures were used for muscle layers and skin. Prior to final closure, the lungs were manually inflated and the chest drain connected to an under water seal. The animal was now laid on its side, warmed in an electric blanket and encouraged to breath spontaneously. Temperature, respiration, pulse, blood pressure and chest drainage were observed and losses replaced accurately. When the dogs survived, arterial and venous cannulae and chest drains were removed after twelve hours. Oral fluids were encouraged after this time and light diet after twenty-four hours. In uncomplicated survivals it was normal for the dog to be exercised after the third day.

The calibration of the perfusion apparatus was checked when the experimental procedure was completed. Flows were recorded at 75 mm. Hg. pressure with the heat exchanger at $0^{\circ}C.$, $15^{\circ}C.$ and $37^{\circ}C.$

CHAPTER III

DEEP HYPOTHERMIA WITHOUT EXTRA-CORPOREAL CIRCULATORY ARREST

ACUTE EXPERIMENTS

In the seven experiments described, the apparatus consisted of the simple respiratory pump, using air for pulmonary ventilation, the small oxygenator and the nine metre cooling coil, primed with dextran. In experiments 5, 6 and 7 the Mark I heat exchanger was used, in place of the coil. Mercury-glass thermometers recorded temperatures in the porta hepatis, the rectum, and on occasion in muscle.

EXPERIMENT 1 31.5.57.

A 15 kg. dog was anaesthetised with 0.25 g. sodium thiopentone, intubated and pulmonary ventilation maintained with the respiration pump. The left femoral artery and vein were exposed, the vein cannulated and a slow infusion of normal saline commenced. A thermometer was placed in the porta hepatis through an abdominal incision which was then sutured and a second thermometer placed 10 cm. in the rectum. The upper mediastinum was exposed through a 3rd interspace thoracotomy and the left subclavian artery, atrium and venae cavae prepared for cannulation. A further 0.125 g. of sodium thiopentone was required during the operative procedure. 5 mg. heparin per kilogram body weight were administered intravenously and the femoral artery cannulated to record arterial pressure. The subclavian artery was cannulated with a 4 mm. catheter and catheters of 6 mm. internal bore inserted into the cavae. Bubbles were removed from the arterial and venous lines. During the 95 minutes this procedure occupied the porta hepatis temperature had fallen from 37.2°C. to 36.2°C. and the rectal temperature from 37.2°C. to 36.0°C.

The extra-corporeal perfusion was started and cooling began immediately. Porta hepatis temperature was reduced to 17°C. in 105 minutes, the corresponding rectal temperature being 20.4°C. At these temperatures the heart continued to beat at a rate of

24/minute with a steady rhythm. Rewarming by gradually increasing the temperature of the heat exchanger to 31.6°C. occupied 148 minutes. At 31.7°C. rewarming and extra-corporeal circulation were discontinued and the atrial catheters removed. A precipitate fall in blood pressure required intra-arterial infusion of 200 ml. of dextran and blood; during the following 30 minutes the porta hepatis temperature fell to 30.2°C. The experiment was terminated at this point.

Temperature, blood pressure and extra-corporeal perfusion rate are shown in Figure 10. Blood samples were removed for plasma haemoglobin estimations and these results are also charted.

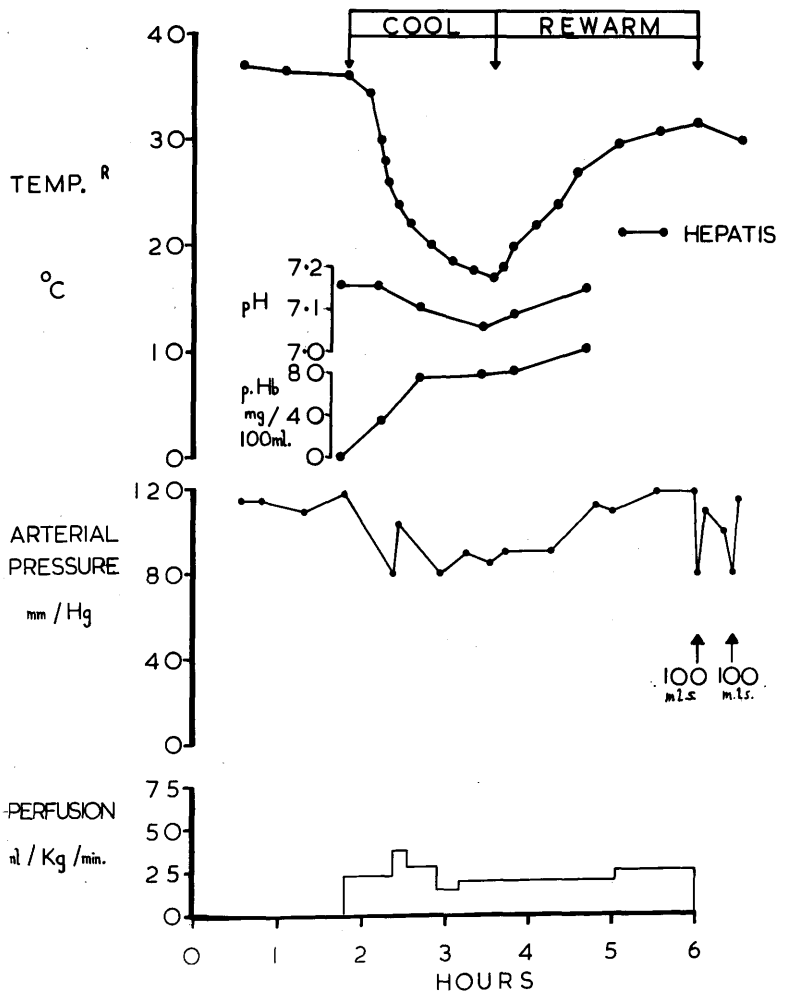


Figure 10.

Observations

1. The heart continued to beat regularly at 17°C. Each beat produced an elevation of 10 mm. on the blood pressure record in addition to the 100 mm. maintained chiefly by the arterial pump.

2. The considerable haemolysis noted was attributed to the prolonged period of extra-corporeal circulation. Dextran may also have contributed to this high level.

3. Increased bleeding from the chest wound was noted during the rewarming and terminal stages of the experiment.

EXPERIMENT 2 4.6.57.

A 15 kg. dog was anaesthetised with 0.5 g. intravenous sodium thiopentone, intubated and respiration maintained with air delivered by the respiration pump. The preparation, temperature recording and cannulation were identical with the previous experiment. 5 mg. heparin per kilogram body weight was given intravenously prior to inserting the arterial cannulae. Both porta hepatis and rectal temperatures were 37°C. when the exposure was completed. Arterial blood samples were taken at intervals for pH and haematocrit estimations. Cooling of the porta hepatis temperature to 7.8°C. (rectal 9.2°C.) was accomplished in 96 minutes; the heart stopped beating at 12.3°C. and remained flaccid. On rewarming the temperature of the heat exchanger was initially raised to 25°C. and thereafter maintained about 10°C. higher than the porta hepatis temperature until the former reached 37°C., at which level it was maintained. No cardiac action was observed until 26.5°C. when the heart was stroked gently and it commenced to beat regularly, with a rapid rise of mean arterial pressure. Rewarming was discontinued at 31.8°C. (rectal 25°C.). On discontinuing extra-corporeal perfusion two intra-arterial infusions of 80 ml. each were required to maintain a satisfactory blood pressure. The animal was observed for 20 minutes thereafter, by which time the porta

hepatis temperature had fallen by 2°C. The porta hepatis temperatures, arterial pressure and extra-corporeal perfusion rate are shown in Figure 11, with the arterial pH and haematocrit. The E.C.G. changes are shown in Figures 12 and 13.

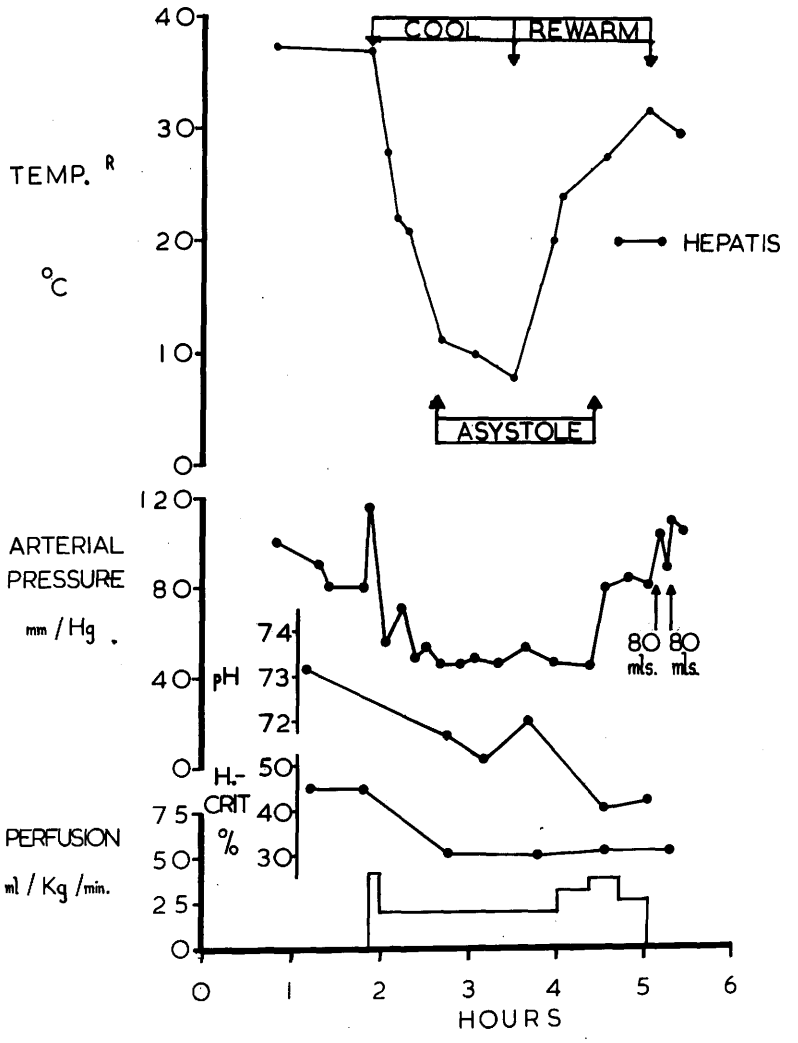


Figure 11.

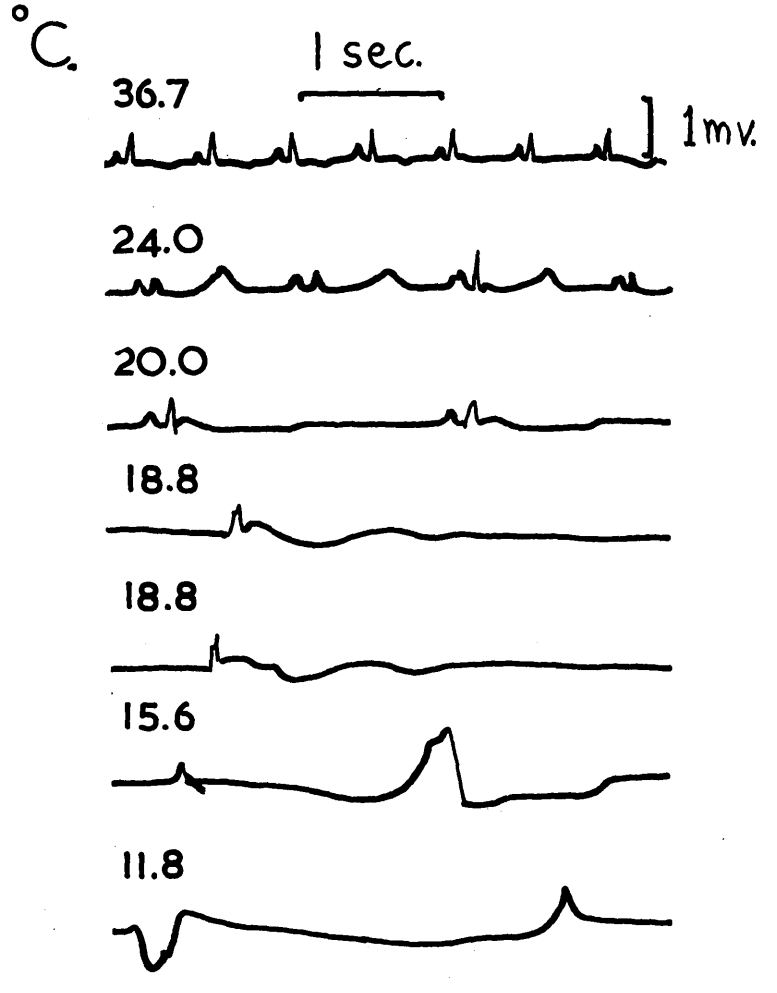


Figure 12. E.C.G. on Cooling.
Porta Hepatis Temperature °C.

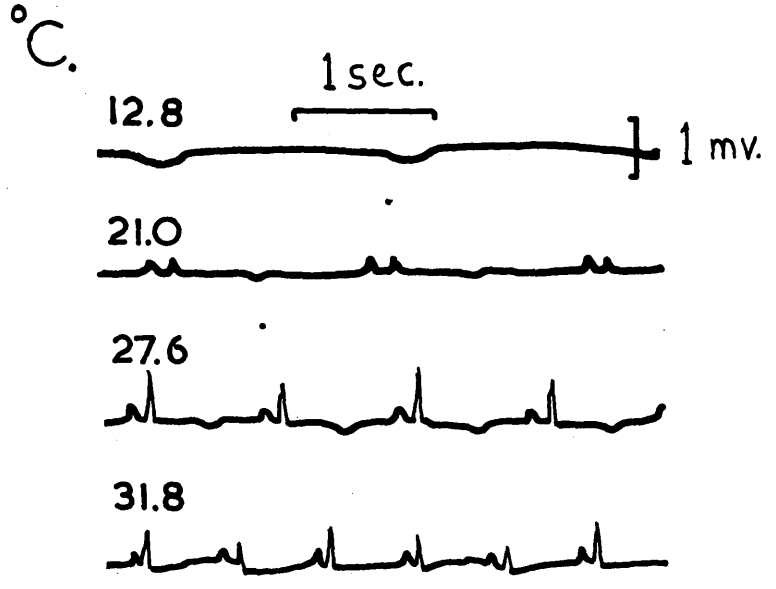


Figure 13. E.C.G. on Rewarming.
Porta Hepatis Temperature °C.

Observations

1. It was possible to cool a 15 kg. dog to a porta hepatis temperature of 7.8°C. and rewarm without ventricular fibrillation. The heart remained flaccid during this period and a gentle stimulus initiated effective systole.

2. Electrical activity persisted despite absence of mechanical systole, during the rewarming period.

3. There was an appreciable fall of arterial pH.

4. The reduction in haematocrit could be attributed to haemodilution with dextran, used for priming the apparatus.

EXPERIMENT 3 6.6.57.

A 16.5 kg. dog was anaesthetised with 0.25 g. intravenous sodium thiopentone and the procedure was identical to that in the previous experiments. An additional 0.1 g. of sodium thiopentone was required during the surgical exposure and when completed, the porta hepatis temperature was 36.2°C. and the rectal temperature 36°C. 5 mg. heparin per kilogram body weight were administered intravenously prior to inserting the catheters. Arterial blood samples were removed at intervals during the experiment. Cooling to 6°C. (rectal 8.7°C.) was accomplished in 66 minutes and the heart continued to beat until a porta hepatis temperature of 8.9°C. was reached. On rewarming the heat exchanger temperature was rapidly raised to 27°C. and the animal quickly rewarmed to 14°C., when ventricular fibrillation was noted. Recooling to 12.8°C. arrested the heart and on subsequent rewarming a normal beat commenced at 14.6°C. Thereafter rewarming to 33°C. was uneventful. A corneal reflex was noted at 22.2°C. The whole rewarming phase occupied 71 minutes and was followed by an after-drop of 4.3°C. which levelled off after 45 minutes (Figure 14). The arterial pressure was maintained at 90 - 95 mm. Hg. during this period. The arterial samples were analysed for pH, tCO_2, haematocrit and plasma haemoglobin and the results are also recorded.

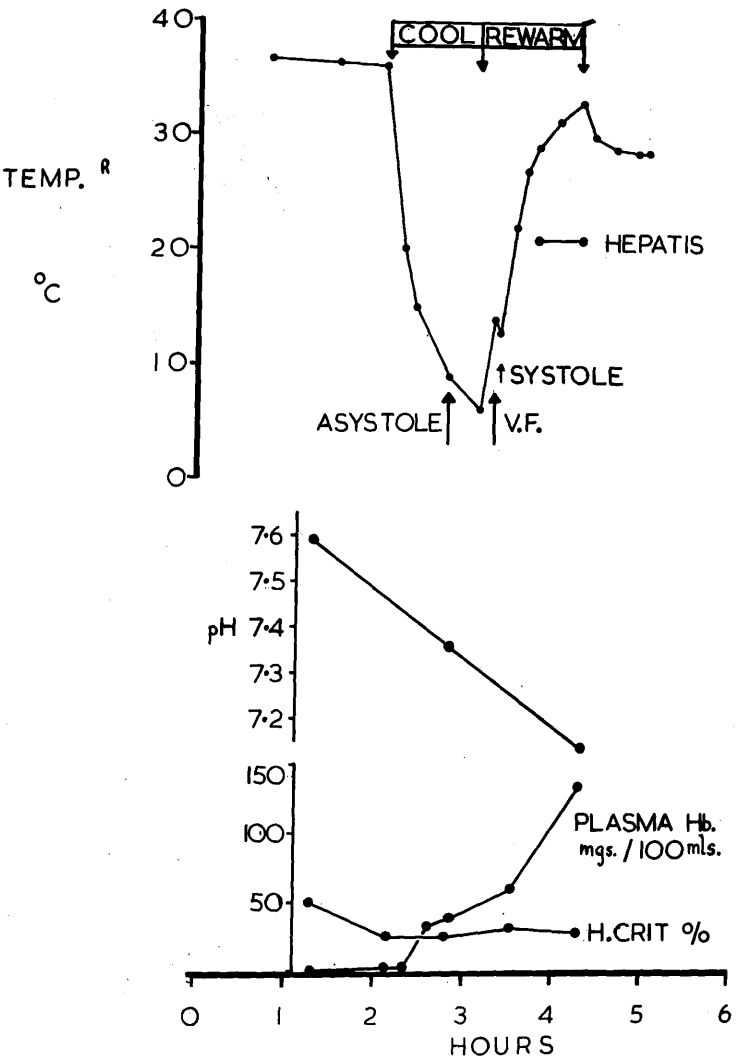

40
30
20
10
0
TEMP. R
°C
COOL
REWARM
HEPATIS
SYSTOLE
ASYSTOLE
V.F.
7·6
7·5
pH 7·4
7·3
7·2
150
100
50
PLASMA Hb.
mgs. / 100 mls.
H.CRIT %
0
1
2
3
4
5
6
HOURS

Figure 14.

Observations

1. Ventricular fibrillation was apparently induced by rapid rewarming of the heat exchanger. Cold arrest was produced by recooling and subsequent rewarming resulted in normal contractions. Thus a "cold conversion" of ventricular fibrillation was achieved.

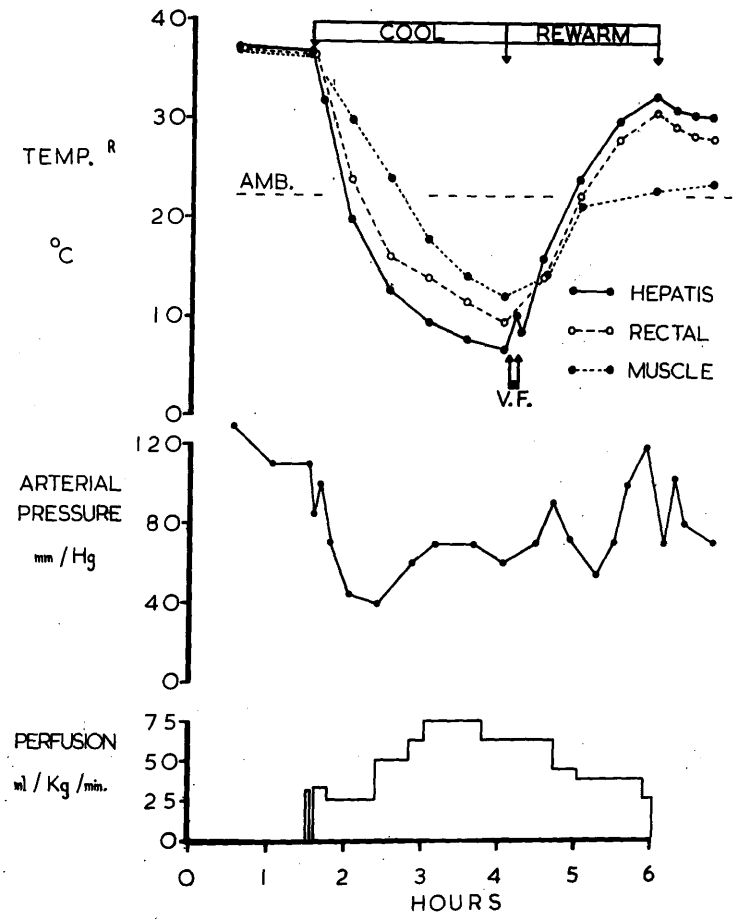
2. On completing the perfusion, the after-drop of temperature ceased after 45 minutes, indicating that metabolism had commenced, despite the anaemia.

3. A considerable degree of haemolysis and acidosis was noted. The low haematocrit values may have contributed to the latter.

EXPERIMENT 4 11.6.57.

A 15.5 kg. dog was anaesthetised with 0.25 g. sodium thiopentone and prepared as in the previous experiments. In addition to the porta hepatis and rectal temperatures, the hind limb adductor muscle temperature was also recorded. 5 mg. heparin per kilogram body weight was administered intravenously prior to cannulation. Cooling from 36.8°C. to 6.7°C. occupied 153 minutes. An initial delay and fall of blood pressure were occasioned by a kinked catheter within the atrium which required adjustment. On rewarming the temperature of the heat exchanger was purposely elevated to 37°C. and ventricular fibrillation resulted. This was converted by rapidly reducing this temperature to 0°C. and with more gradual rewarming a normal cardiac contraction was restored. Thereafter rewarming to 32.4°C. was completed in 123 minutes, to be followed by an after-drop of 2.4°C. This levelled off after 45 minutes and muscle temperature was observed to be rising during this period.

Porta hepatis, rectal and muscle temperatures are plotted with arterial pressure and perfusion rate in Figure 15, and the relevant E.C.G. trace is shown in Figure 16.


40
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TEMP. R
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REWARM
AMB.
HEPATIS
RECTAL
MUSCLE
V.F.
120
80
40
0
ARTERIAL
PRESSURE
mm / Hg
75
50
25
0
PERFUSION
ml / Kg /min.
0
1
2
3
4
5
6
HOURS

Figure 15.

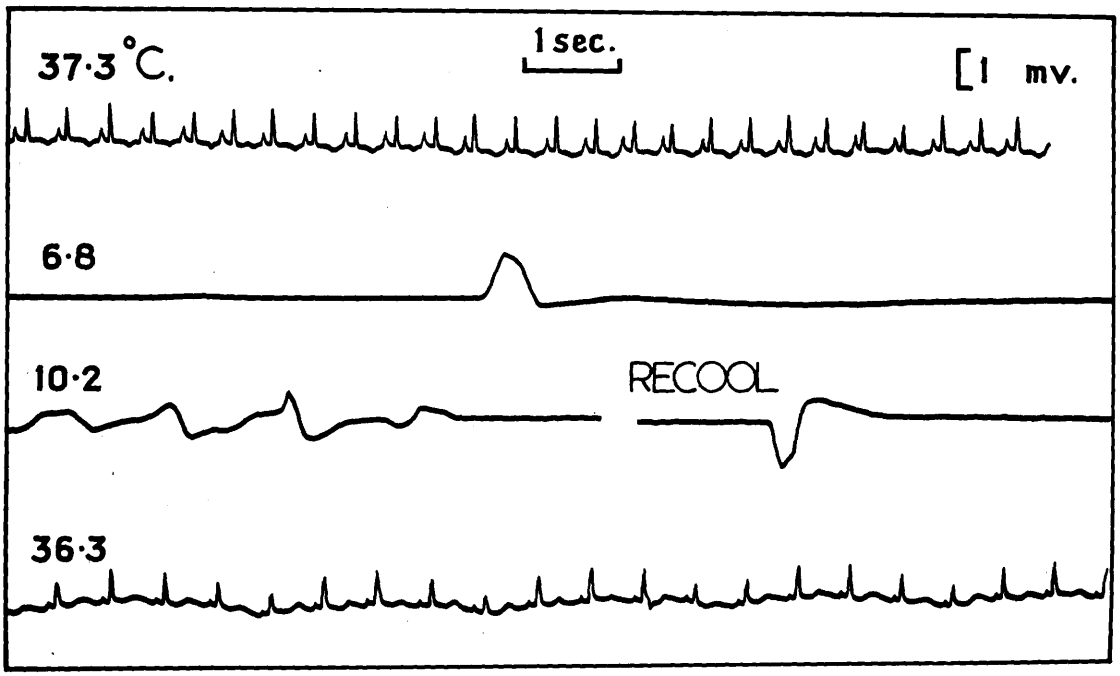

Figure 16.

Observations

1. The cold conversion of ventricular fibrillation observed in the previous experiment was confirmed.

2. Rising muscle temperatures during the after-drop period suggested redistribution of heat in the body and might in part account for the after-drop.

EXPERIMENT 5 12.6.57.

A 16 kg. dog was anaesthetised with intravenous 0.5 g. sodium thiopentone, intubated and respirated. Additional sodium thiopentone totalling 0.1 g. was required during the surgical exposure. 5 mg. heparin per kilogram body weight were administered intravenously prior to cannulation of the vessels. Porta hepatis, rectal and thigh adductor muscle temperatures were observed as in the previous experiment. The second heat exchanger (Mark I), described in Chapter II, was incorporated in the circuit for this experiment; otherwise the apparatus was unchanged and primed with dextran as in previous experiments. During the operation porta hepatis, rectal and muscle temperatures had fallen from 36.8°C., 36.5°C. and 35.8°C. to 34.4°C., 34.3°C. and 33.3°C. respectively. Cooling of these temperatures to porta hepatis 4.7°C., rectal 6°C. and muscle 9.9°C. was obtained in 94 minutes, and rewarming to 35.2°C., 33.0°C. and 20.2°C. respectively, in a further 96 minutes. Cardiac asystole occurred from 11.8°C. to 15.7°C. on rewarming, a duration of 93 minutes. On rewarming brisk corneal reflexes were noted at 22°C., knee jerks at 30°C. and after the perfusion was discontinued spontaneous respiration occurred at 28.9°C. The blood pressure was well maintained during this period and no serious bleeding from the wounds was noted. 200 ml. of dextran had been added to the circulation during this perfusion.

Observations

1. The Mark I heat exchanger, combined with higher flow rates, permitted more rapid cooling and rewarming, as shown in Figure 17.

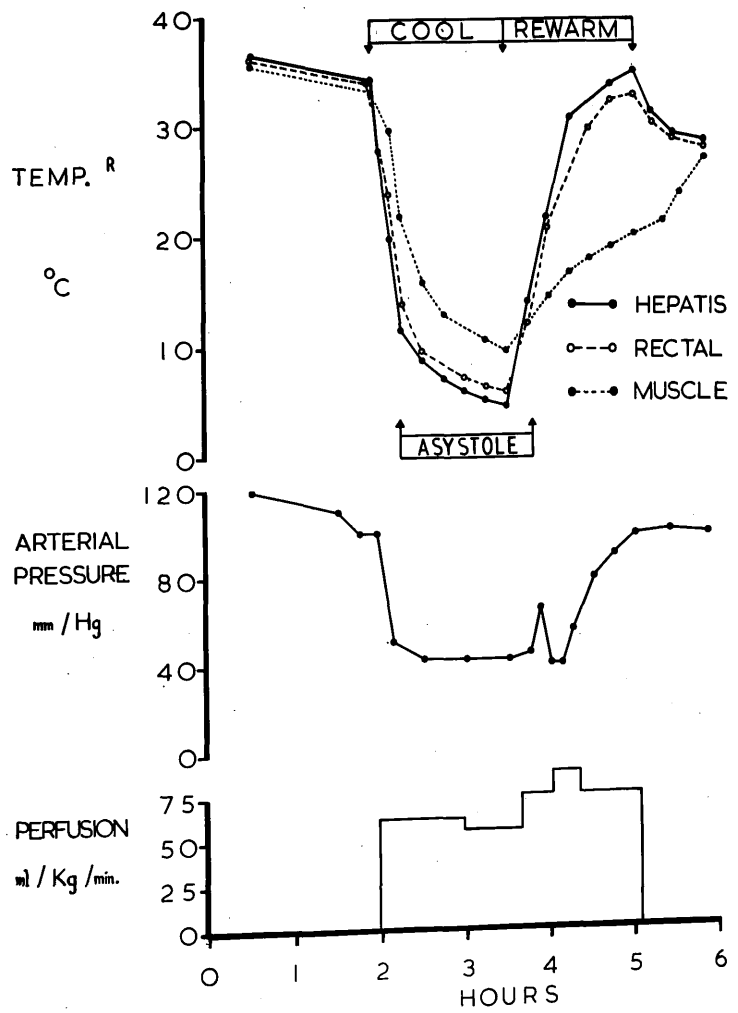

Figure 17

EXPERIMENT 6 14.6.57.

A 17 kg. dog was anaesthetised with 0.6 g. sodium thiopentone with additional dosage of 0.3 g. during the surgical procedure. No alteration was made in the method, and porta hepatis, rectal and muscle temperatures were recorded. The Mark I heat exchanger was incorporated in the extra-corporeal circulation circuit. Cooling from a porta hepatis temperature of 35.7°C. to 6.0°C. took 51 minutes and rewarming to 33°C., 76 minutes. Cardiac asystole occurred at 11.0°C. and normal contractions recommenced at 12.5°C. on rewarming, a total period of 39 minutes. 200 ml. of dextran were added during cooling, and a further 200 ml. during rewarming. Blood pressure was well maintained on discontinuing the bypass and the after-drop of 3.4°C. remained stationary after 18 minutes.

Observations

1. The heart remained empty during the whole perfusion and was flaccid during the 39 minutes cold arrest. This was attributable to the relatively large bypass circulation.

2. Additional dextran, total 400 ml., was accepted into the circulation without embarrassment. Blood losses during this period did not exceed 100 ml.

EXPERIMENT 7 19.6.57.

A 15 kg. dog was anaesthetised with 0.6 g. of sodium thiopentone and 0.1 g. used to maintain anaesthesia subsequently. 5 mg. heparin per kilogram body weight was administered prior to arterial cannulation, and surgical exposure and experimental procedure were identical with the previous experiment.

The porta hepatis temperature was lowered from 35.5°C. to 5.8°C. in 63 minutes. A short period of ventricular fibrillation was observed between 13.6°C. and 9.6°C. after which a slow normal beat was resumed. Asystole occurred at 8.7°C. and continued until 11.8°C. on rewarming, a period of 36 minutes. Rewarming to 33°C. occupied 93 minutes. 100 ml. of dextran were added to the circulation during cooling and rewarming.

Observations

1. Very active corneal reflexes and attempts at spontaneous respiration were noted during the rewarming period.

2. There was no apparent cause for ventricular fibrillation on cooling. Spontaneous conversion occurred with further cooling.

CHAPTER IV

DEEP HYPOTHERMIA WITHOUT EXTRA-CORPOREAL CIRCULATORY ARREST

SURVIVAL EXPERIMENTS

PART I

The apparatus used in the experiments described consisted of the modified respiratory pump, the large oxygenator and either Mark I or Mark II heat exchangers. The apparatus was primed with fresh donor blood and full aseptic precautions were taken during the experimental procedure. In this series the experimental dogs were prepared with 125 mg. aureomycin on each of the two days preceeding the experiment. Atropine g. 1/200 was given intravenously prior to induction of anaesthesia.

Two control experiments were performed to test innovations in the extra-corporeal circulation, particularly the heat exchangers.

CONTROL EXPERIMENTS

The first experiment was performed with the Mark I heat exchanger before commencing the initial experiment of this series. A 10.5 kg. dog was anaesthetised, intubated and respiration maintained with the respiratory pump. The chest was opened with a transverse 3rd space thoracotomy and after administering 5 mg. heparin per kilogram body weight the vessels were cannulated as previously described. Femoral arterial pressure and porta hepatis and rectal temperatures were recorded. The dog was perfused at a rate of 53 ml. per kilogram per minute for 62 minutes, the heat exchanger being maintained at a constant 37°C. For 25 minutes of this period, tapes previously passed round the superior and inferior venae cavae were tightened to complete the cardiac bypass. On completing the experiment, catheters and thermocouples were removed and the chest closed in layers. The dog recovered consciousness in $3\frac{1}{2}$ hours and made a satisfactory recovery. Haemolysis over the total perfusion period was 45 mg. per 100 ml. The animal was sacrificed on the 18th day on account of an empyema thoracis which drained through the chest wound. After this, and the experience of the first two experiments, the exposure described by Andreason and Watson was subsequently used for transverse thoracotomy incisions.

The second control experiment was interposed between survival experiments 9 and 10 to test the Mark II heat exchanger. This was performed on an 11.5 kg. bitch, the procedure being identical to that described above, with the exception of the method of chest exposure and Mark II heat exchanger. This animal made an uninterrupted recovery and was observed for three months. Total haemolysis was 49 mg. per 100 ml. over a 64 minute perfusion at a mean rate of 63 ml. per kilogram per minute.

There was no appreciable change in the porta hepatis, rectal or muscle temperatures during the perfusion in either of these control experiments.

EXPERIMENT 1 30.8.57.

A 15 kg. dog was anaesthetised with 0.3 g. sodium thiopentone, intubated and respiration maintained with a 50 : 50 nitrous oxide, oxygen mixture delivered by the modified respiratory apparatus previously described. Additional pethidine totalling 50 mg. was given during the experiment. The right femoral vein was cannulated and a slow drip of 0.9 per cent saline commenced. A thermocouple was inserted 10 cm. into the rectum. A transverse 3rd space thoracotomy was performed under full aseptic precautions and the left subclavian artery and the right atrium prepared for catheterisation. A thermocouple was placed in the porta hepatis through a small epigastric incision. Thermocouples were also placed in the adductor muscle of thigh and subcutaneously in the groin. 5 mg. heparin per kilogram body weight was administered intravenously and the subclavian artery cannulated. The tubing was connected to the extra-corporeal perfusion apparatus and air bubbles evacuated. The venae cavae were catheterised with flexible cannulae via atrial stab incisions and previously inserted purse string sutures drawn tight. The catheters were connected through a Y piece to the venous syphon leading to the oxygenator through a fall of 15 cm. The large oxygenator was used leading to the Mark I heat exchanger, thence by a bubble trap to the

arterial cannulae. The apparatus was primed with donor dog blood containing 40 mg. heparin per litre, and oxygenated with 95 per cent oxygen, 5 per cent carbon dioxide. After removing bubbles from the venous line, the extra-corporeal circulation was commenced. Arterial pressure was stabilised at 70 mm. Hg. and hypothermia induced by lowering the temperature of the heat exchanger coolant from 37°C. to -1°C. A porta hepatis temperature of 8°C. was reached in 36 minutes and rewarming to 33°C. occupied a further period of 37 minutes. Cardiac asystole occurred at 16.2°C. and recommenced at 14°C. on rewarming, a period of 29 minutes. Porta hepatis, rectal and skin temperatures, blood pressure and perfusion rate are recorded in Figure 18, and the E.C.G. in Figure 19.

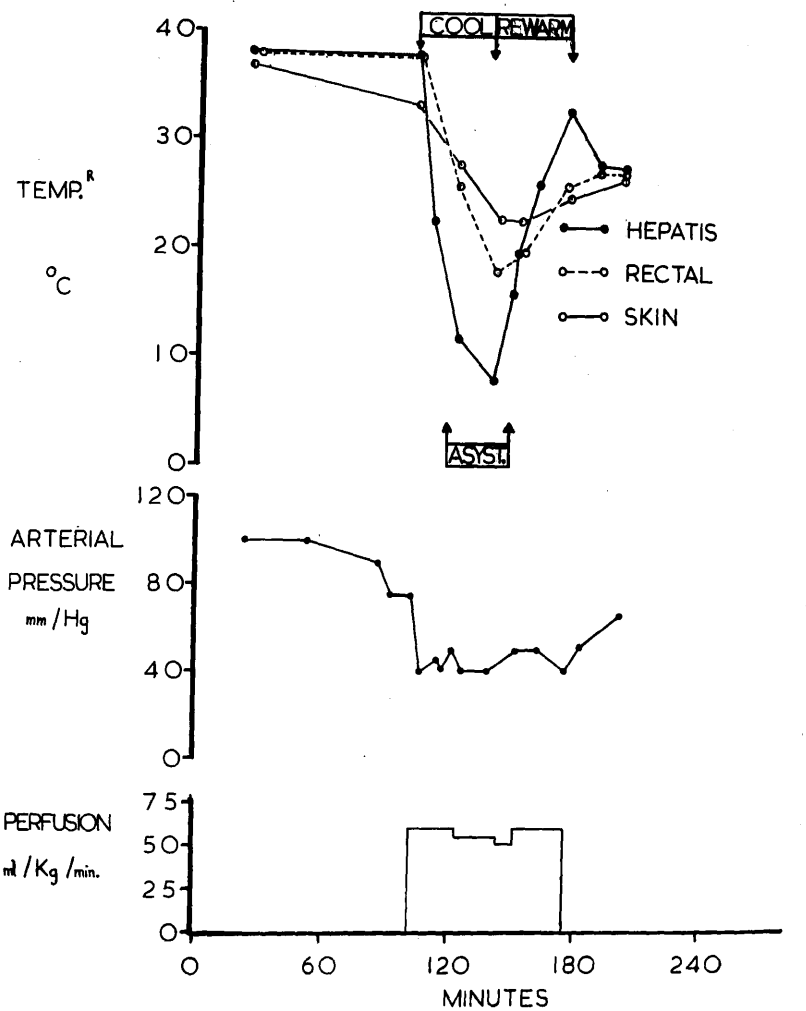
COOL
REWARM
ASYST.
TEMP.R
°C
40
30
20
10
0
HEPATIS
RECTAL
SKIN
ARTERIAL
PRESSURE
mm/Hg
120
80
40
0
PERFUSION
ml/Kg/min.
75
50
25
0
0
60
120
180
240
MINUTES

Figure 18.

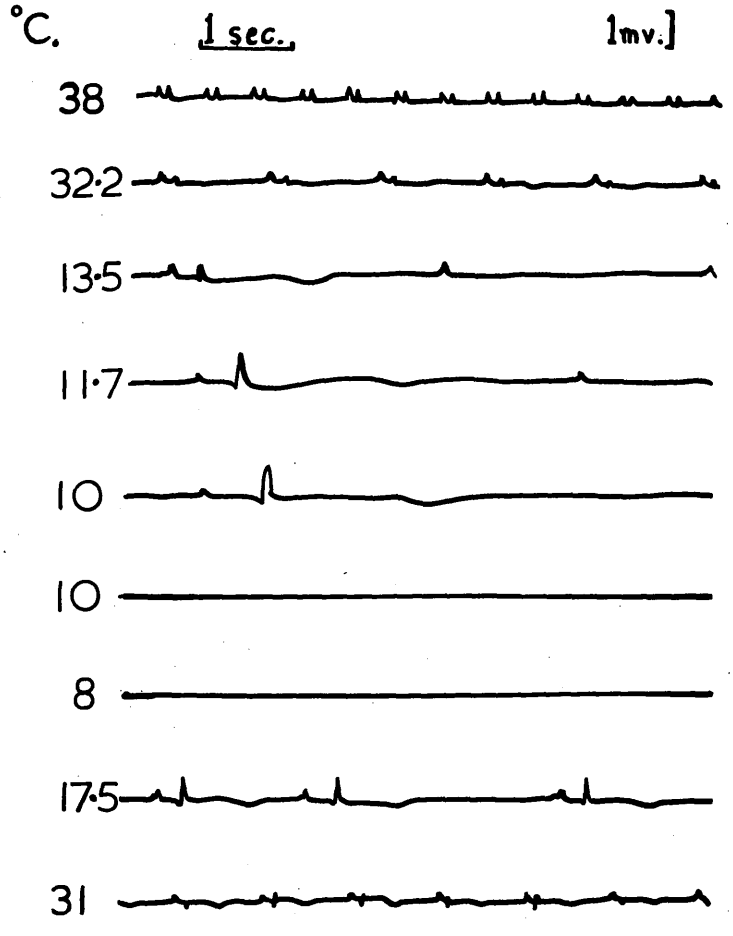

Figure 19.

The caval and subclavian cannulae were removed and 5 mg. protamine sulphate per kilogram body weight given intravenously. The chest wound was closed with drainage to an underwater seal and all thermocouples with the exception of the rectal, removed. During the 25 minutes this occupied the porta hepatis temperature had fallen 5.2°C. Thereafter the rectal temperature slowly rose to 40°C. over the next $5\frac{1}{2}$ hours, when the dog recovered consciousness. During this period 200 ml. of blood and 150 ml. of 1/250,000 noradrenaline were infused intravenously and 300 ml. of blood drained from the chest. The chest drain was removed after 12 hours, and a further 30 ml. aspirated 6 hours later. After a stormy convalescence the dog recovered and was eating on the third day. An empyema thoracis subsequently developed and discharged through the chest wound, and the dog was sacrificed on the 14th day. Post mortem showed a ventral empyema cavity in the chest and pericarditis. All organs were pale but otherwise normal.

EXPERIMENT 2 4.9.57.

A 10 kg. bitch was anaesthetised with 0.25g. intravenous sodium thiopentone, and the subsequent procedure was identical with that for the previous experiment. On cooling a porta hepatis temperature of 4.5°C. was reached in 35 minutes and rewarming to 33.3°C. occupied 45 minutes, as recorded in Figure 20.

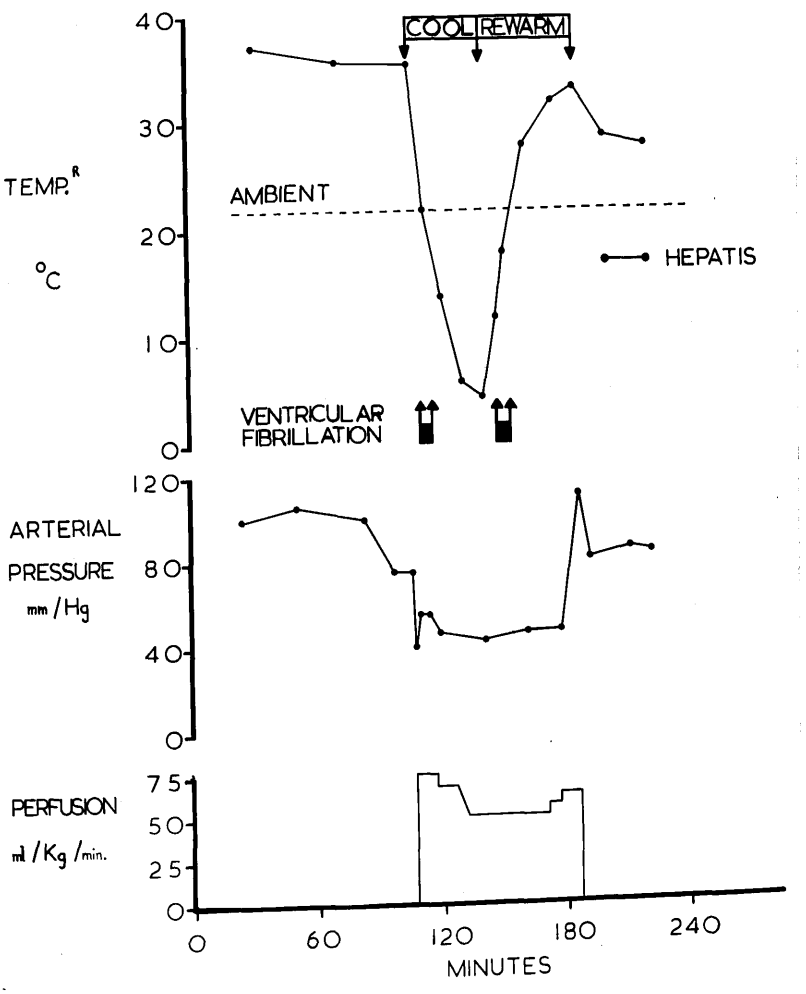

Figure 20

On cooling ventricular fibrillation was observed between 24°C. and 18°C., when it converted spontaneously; on rewarming it recurred between 12°C. and 23°C. Conversion to normal rhythm again occurred spontaneously (Figure 21).

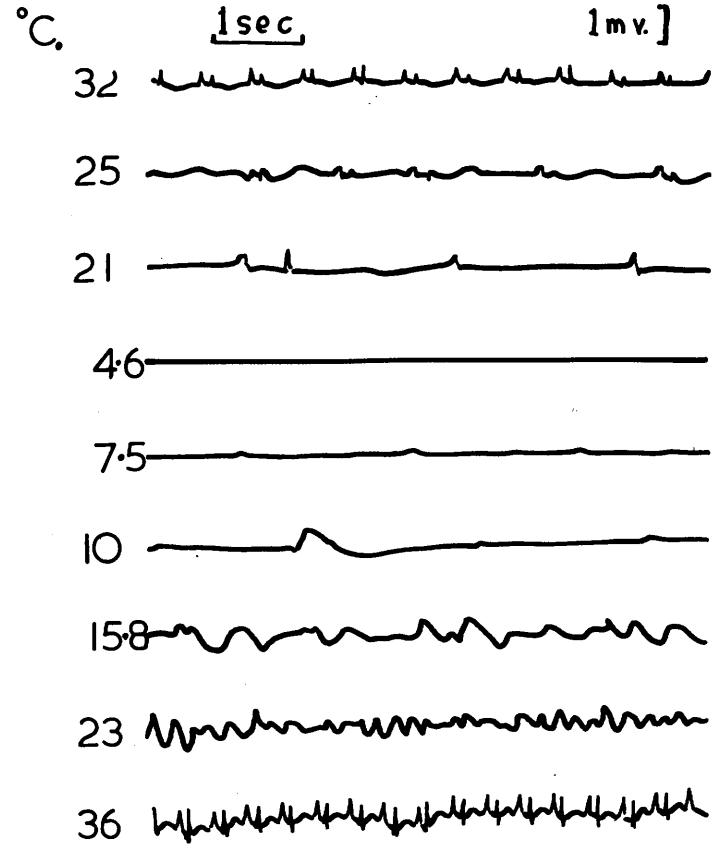

Figure 21

During the post-operative period the animal rewarmed to a rectal temperature of 40°C. in 7 hours and had a relatively smooth recovery. She later developed an empyema thoracis and was sacrificed on the 10th day. Post mortem examination confirmed the presence of an empyema cavity and apart from pallor of all organs, there was no other macroscopic abnormality.

EXPERIMENT 3 6.9.57.

A 10 kg. bitch was anaesthetised, prepared for experiment in the same manner as experiments 1 and 2, with the exception of the Andreason and Watson chest exposure. Cooling to a porta hepatis temperature of 12°C. took 40 minutes and rewarming to 33.2°C. occupied a further 40 minutes. Cardiac asystole occurred at 18°C. on cooling to 13.5°C. on rewarming, a period of 35 minutes. The temperature chart is reproduced in Figure 22.

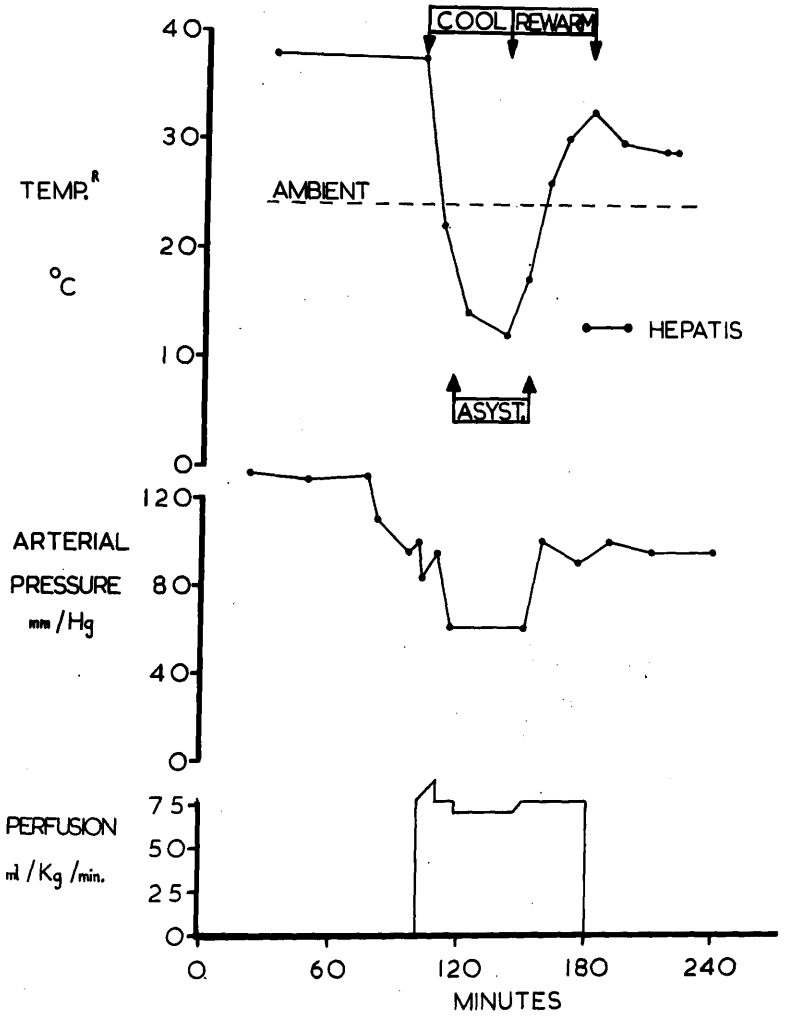
COOL
REWARM
40
30
20
10
0
TEMP.R
°C
AMBIENT
HEPATIS
ASYST.
120
80
40
0
ARTERIAL
PRESSURE
mm/Hg
75
50
25
0
PERFUSION
ml/Kg/min.
0
60
120
180
240
MINUTES

Figure 22

A fall of 4.5°C. occurred over 45 minutes and thereafter the rectal temperature slowly rewarmed to 40°C. over the following 6 hours. 300 ml. of blood drained from the chest during this period and were replaced by 200 ml. of donor blood, dextran and noradrenaline were also used to maintain arterial pressure. The dog died after 12 hours without regaining consciousness. At post mortem there was no evidence of a bleeding point and all ligatures were intact. The organs were pale without evidence of other pathological change.

Observations

1. There was apparently no variation in technique or post-operative care from the two previous experiments.

2. Considerable post-operative haemorrhage occurred from all wounds and insufficient donor blood was available.

EXPERIMENT 4 12.9.57.

A 15 kg. dog was anaesthetised and prepared as previously described, with the exception that only porta hepatis and rectal temperatures were observed. On cooling a porta hepatis temperature of 4.8°C. was reached in 35 minutes and rewarming to 34.4°C. occuplied 45 minutes. Cardiac asystole was noted at 15.4°C. on cooling and persisted to 14.8°C. on rewarming, a period of 25 minutes. After discontinuing the extra-corporeal circulation, the rectal temperature fell from 31.2°C. to 29.3°C., after which the animal rewarmed slowly to 37°C. Haemorrhage from the chest drains totalled 450 ml. and dextran was used to supplement the 200 ml. of blood available. The dog died 6 hours and 30 minutes after completing the experiment. Post mortem showed anaemia of all organs and pulmonary collapse.

Observations

1. Excessive post-operative haemorrhage.

2. Poor pulmonary ventilation required frequent manual inflation of the lungs during the post-operative period.

EXPERIMENT 5 4.10.57.

A 14 kg. dog was anaesthetised and the preparation was similar to the previous experiments. Porta hepatis and rectal temperatures were recorded and on commencing cooling, the former was reduced to 6.3°C. in 38 minutes. Rewarming to 34.3°C. occupied 49 minutes and was followed by an after-drop of 5.7°C. over 51 minutes. Asystole occurred at 12°C. on cooling and normal rhythm returned at 14.9°C. on rewarming. During the post-experimental period rewarming to a rectal temperature of 37.5°C. took a further period of 4 hours. When this temperature was 33°C. a sample of venous blood showed a clotting time of 10 minutes. 5 mg. protamine sulphate per kilogram body weight had been given on completing the experiment, and this dose was now repeated, but without effect on the clotting time of the blood. During this period 100 ml. of blood drained from the chest. The dog suddenly collapsed and died 7 hours after completing the experiment.

At post mortem there were approximately 250 ml. of blood in the chest which had failed to drain and massive atelectasis of both lungs. All organs were pale but otherwise normal.

EXPERIMENT 6 10.10.57.

A 12.5 kg. dog was anaesthetised, prepared as previously described and cooled to a porta hepatis temperature of 8°C. in 30 minutes. On cooling, ventricular fibrillation occurred between 17.5°C. and 13.5°C. after which cardiac action ceased. On rewarming normal contraction was observed at 13.8°C. Rewarming to 34°C. occupied 65 minutes and was followed by an after-drop of 3.5°C. over 75 minutes. When the experiment was completed 5 mg. protamine sulphate per kilogram body weight were administered. A subsequent blood coagulation time was 10 minutes. A titration of a further 1 mg. of protamine sulphate per kilogram was repeated on 6 occasions but failed to reduce the time below 9 minutes after any one administration.

The animal collapsed and died 4 hours after completing the experiment, the rectal temperature having reached 32.5°C.

Post mortem showed massive atelectasis and 200 ml. of blood in the chest. Apart from pallor of the organs there was no abnormality.

EXPERIMENT 7 11.10.57.

A 10.5 kg. bitch was anaesthetised and the experimental procedure repeated. Cooling to a porta hepatis temperature of 9.5°C. was completed in 32 minutes, and followed by rewarming to 34°C. in 47 minutes. An after-drop of 6°C. occurred over the following 58 minutes to be followed by slow rewarming to a rectal temperature of 31.5°C. in 6 hours. The coagulation time of the blood after 5 mg. protamine sulphate per kilogram body weight was 10 minutes and, as in the previous experiment, this did not decrease on repeating the protamine sulphate titration. The animal ventilated poorly and died suddenly after 6 hours. Post mortem changes were similar to those previously described.

EXPERIMENT 8 24.10.57.

The experiment was repeated on an 11 kg. dog in the manner previously described. Cooling to a porta hepatis temperature of 4.7°C. was accomplished in 55 minutes and rewarming to 35.4°C. in 50 minutes. An after-drop of 7.7°C. occurred and the dog died suddenly, apparently of cardiac arrest, 2 hours after completing the experiment. A blood film taken shortly before this occurred, was subsequently stained with haematoxylin and eosin and when examined, showed a complete absence of platelets and white blood cells.

EXPERIMENT 9 7.11.57.

A 10 kg. bitch was anaesthetised and the experimental procedure conducted as previously described. Arterial blood samples were taken at intervals during the experiment and analysed for sodium, potassium, haemoglobin, plasma haemoglobin and serum osmolarity. Haemotoxylin and eosin stained films were also examined for platelets and white cells. The plasma fibrinogen content was analysed on two specimens. These results are plotted against temperature in Figure 23.

The animal was cooled to a porta hepatis temperature of 10.5°C. in 35 minutes and rewarmed to 32.7°C. in 45 minutes. Cardiac asystole occurred at 13.5°C. on cooling and contractions were observed at 15.8°C. on rewarming, a period of 21 minutes. On completing the perfusion, the temperature fell 4.2°C. in 4 hours, 15 minutes. Spontaneous respiration was slow to commence, but satisfactory by this time. The dog rewarmed slowly and reached a rectal temperature of 39°C. in 9 hours, 30 minutes, by which time it was fully conscious. Blood pressure and respiration were satisfactory. Chest drainage was 150 ml. and was replaced with 200 ml. of donor blood intravenously during the post-operative period. The animal suddenly collapsed and died 17 hours 30 minutes after completing the perfusion.

Post mortem examination showed 300 ml. of blood in the

chest and patchy collapse of the left lung. Other organs were somewhat pale but otherwise normal. Histological sections showed diffuse polymorph infiltration in all organs. The lungs contained large gram positive bacilli resembling Cl.Welchii, but without inflammatory reaction. All other organs were normal.

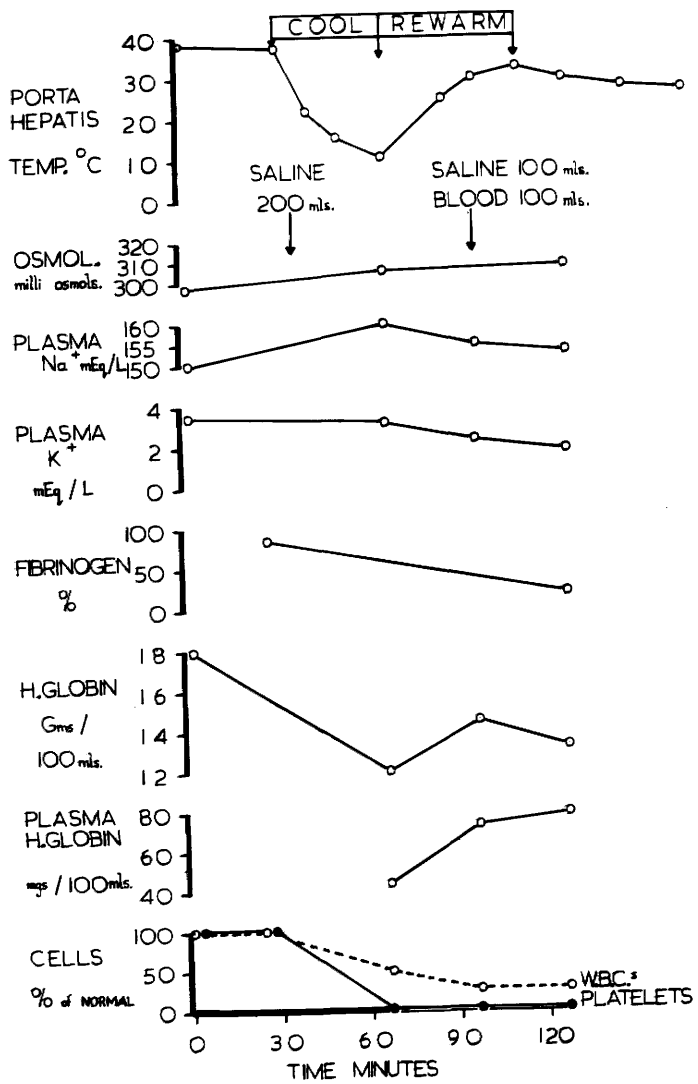

Figure 23

Observations

1. The most striking fact was the reduction of plasma fibrinogen from 80 per cent to 20 per cent of normal, and the absence of platelets and white blood cells.

2. Changes in plasma sodium and osmolarity could be accounted for by the addition of isotonic saline to the oxygenator during cooling and rewarming which had been normal practice to date.

3. There was no apparent explanation why the dogs survived in experiments 1 and 2 since the technique had been identical, if anything improved by experience in the later experiments.

4. In view of the changes in the clotting factors it was decided to increase the heparin dosage to 10 mg. per kilogram body weight in subsequent experiments. Reduction of extracorporeal perfusion time also appeared to be desirable and the Mark II heat exchanger was therefore prepared.

EXPERIMENT 10 12.12.57.

An 11 kg. dog was anaesthetised and prepared as previously described. The Mark II heat exchanger was incorporated in the apparatus and the dosage of heparin increased to 10 mg. per kilogram body weight. A porta hepatis temperature of 5°C. was reached in 32 minutes, and rewarming to 34.6°C. occupied 40 minutes. Arterial samples were removed during this period for sodium potassium, haemoglobin and plasma haemoglobin estimations. Platelets and white cells were also observed from stained blood films, and the results plotted against temperature in Figure 24.

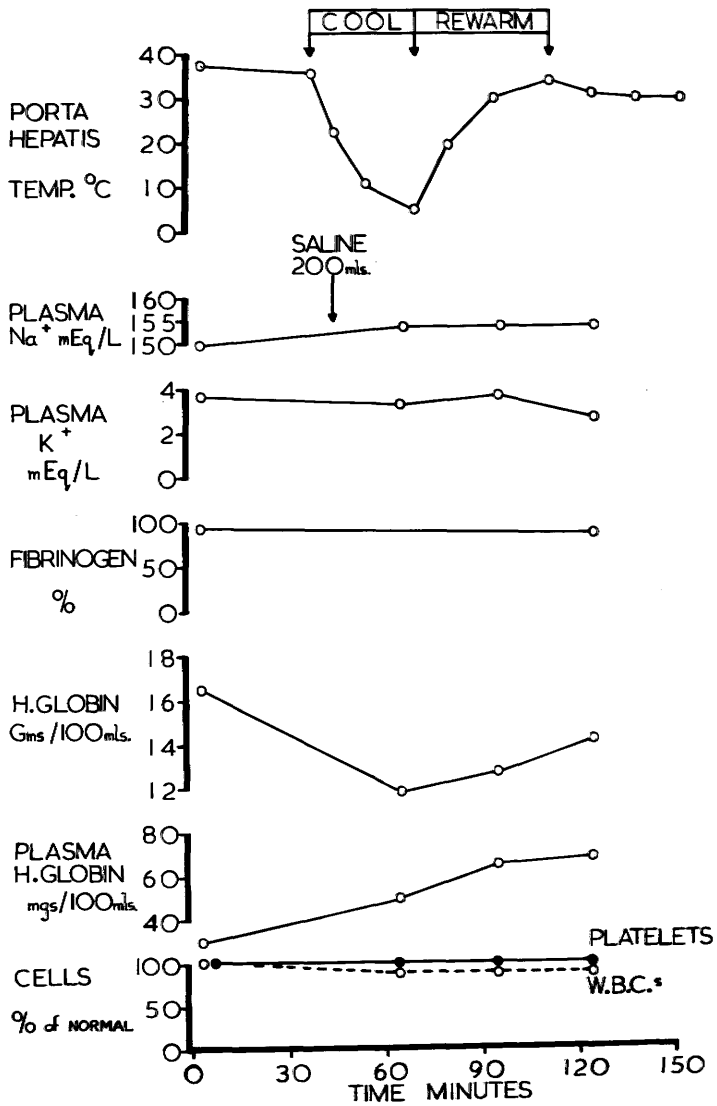
COOL
REWARM
PORTA HEPATIS TEMP. °C
40
30
20
10
0
SALINE 200mls.
PLASMA Na+ mEq/L
160
155
150
PLASMA K+ mEq/L
4
2
0
FIBRINOGEN %
100
50
0
H.GLOBIN Gms/100mls.
18
16
14
12
PLASMA H.GLOBIN mgs/100mls.
80
60
40
PLATELETS
W.B.C.s
CELLS % of NORMAL
100
50
0
0
30
60
90
120
150
TIME MINUTES

Figure 24.

An after-drop of 5.5°C. occurred over the first 2 hours and thereafter rewarming to a rectal temperature of 36°C. occurred in the following 7 hours. Coagulation time was 5 minutes and 200 ml. of blood drained from the chest was replaced intravenously. While being turned to the opposite side the dog suddenly collapsed and died. Post mortem showed patchy collapse in both lungs and slight pallor of organs. There was approximately 50 ml. of blood in the chest.

Observations

1. Platelets and white blood cells were normal, following the increased heparin administration.

2. There was no apparent cause of death.

EXPERIMENT 11 9.1.58.

A 12 kg. bitch was anaesthetised and prepared as in the previous experiment. Cooling to a porta hepatis temperature of 7.2°C. occupied 38 minutes and rewarming to 36°C. a further 37 minutes. After completing the experiment the rectal temperature fell 2.5°C. to 28°C. over 80 minutes and rewarming to 36.6°C. followed during the next 10 hours. Coagulation time was 5 minutes with satisfactory clot retraction. The dog died 1 hour and 45 minutes later. During the post-operative period a loss of 150 ml. of blood from the chest was replaced with 200 ml. donor blood intravenously. Post mortem showed no features differing from those in previous experiments. There was a minimal quantity of blood in the chest and a few areas of collapse in both lungs.

EXPERIMENT 12 16.1.58.

A 13.5 kg. dog was anaesthetised and prepared for perfusion as before. Cooling to a porta hepatis temperature of 6.4°C. occupied 30 minutes and rewarming to 36.7°C. a further 43 minutes. An after-drop in rectal temperature from 31.5°C. to 29.5°C. occurred over 2 hours and subsequently rose to 38°C. in 7 hours. During the rewarming stage spontaneous pulmonary ventilation was inadequate and the lungs required manual inflation. Blood coagulation times and clot retraction were normal. The dog died suddenly 7 hours 30 minutes after completing the experiment.

Post mortem showed a collapse of the left lung with a minimal effusion of blood in the chest.

In experiments 10, 11 and 12 the blood coagulation problems had been overcome but nevertheless the animals failed to ventilate adequately during the post-operative period; this did not explain the survival in experiments 1 and 2. A few of the relevant observations are tabulated below.

	PERFUSION				RECOVERY		
Expt. No.	Time mins.	Porta Hepatis Temp. °C. Cool	Rewarm	Afterdrop	Rectal Temp. °C.	12am Temp. Croydon	Survival Time Hrs.
1	73	8	33	5.3	40	12.8	Survived
2	80	4.5	32	4	40	16.7	Survived
3	80	12	33.2	4.5	40	9.5	12
4	90	4.8	34.4	5.1	37	7.2	6.5
5	89	6.3	34.3	5.7	37.5	12.8	7
6	95	8	34	3.5	32.5	9.5	4
7	79	9.5	34	6	31.5	13.9	6
8	105	4.7	35.4	7.7	28	12.8	2
9	80	10.5	32.7	3.2	29	4.4	17.5
10	72	5	34.6	6.5	36	9.5	7
11	75	7.2	36	8.	37	6.1	11.75
12	73	6.4	36.7	7.2	38	2.2	7.5

At this time it was customary when the operative procedure was completed, to transfer the experimental animal from the operating theatre to a recovery room, heated by a small electric radiator. Additional heat was supplied by an electric blanket. It was now recalled that the first two experiments had been performed on particularly warm days in late summer, and the later experiments during autumn and mid winter. A comparison of the

survival time with the midnight ambient temperature recorded at Croydon, seven miles distant, was not significant; more significant was the survival of 17.5 hours in experiment No.9, when the dog was observed in the relatively warm operating theatre during the recovery period. Thus it appeared that the animals were being insufficiently rewarmed. The technique was slightly modified and a further series of experiments performed.

PART II

The modifications of technique in this group of experiments were:

1. The heat exchanger temperature was rapidly raised to 40 - 41°C. soon after cardiac action commenced and the perfusion continued until the temperature of the porta hepatis was stabilised at 40°C. for 5 to 15 minutes. In experiment 13 this time was extended to 38 minutes whilst ventricular fibrillation was being converted.

2. During rewarming and the early recovery period, an infra-red radiant heater was suspended approximately 40 cm. above the experimental animal. The heater consisted of three elements totalling 1750 watts.

EXPERIMENT 13 21.4.58.

An 17 kg. dog was anaesthetised with 0.3 g. sodium thiopentone given intravenously, and the preparation performed as previously described. 10 mg. heparin per kilogram body weight were administered intravenously prior to cannulating the subclavian artery and the venae cavae. Porta hepatis, rectal and muscle temperatures were observed. On cooling the porta hepatis temperature was reduced to 4.5°C. in 22 minutes. Cardiac asystole occurred at 14.5°C. On rewarming, the temperature of the heat exchanger was raised to 25°C. and the infra-red heater suspended over the dog, 40 cm. above the chest. Ventricular fibrillation was observed on E.C.G. trace at 15°C. and continued throughout rewarming. The heat exchanger temperature was raised by stages to 41°C. and the porta hepatis temperature reached 40°C. after 35 minutes. Electrical defibrillation of the heart was then attempted but failed due to a fault in the apparatus. 2 ml. of potassium citrate were then injected into the aorta and the fibrillation converted. The perfusion was then discontinued after a total running time of 92 minutes, and the chest closed as previously described.

Temperature, arterial pressure and perfusion rate are recorded in Figure 25.

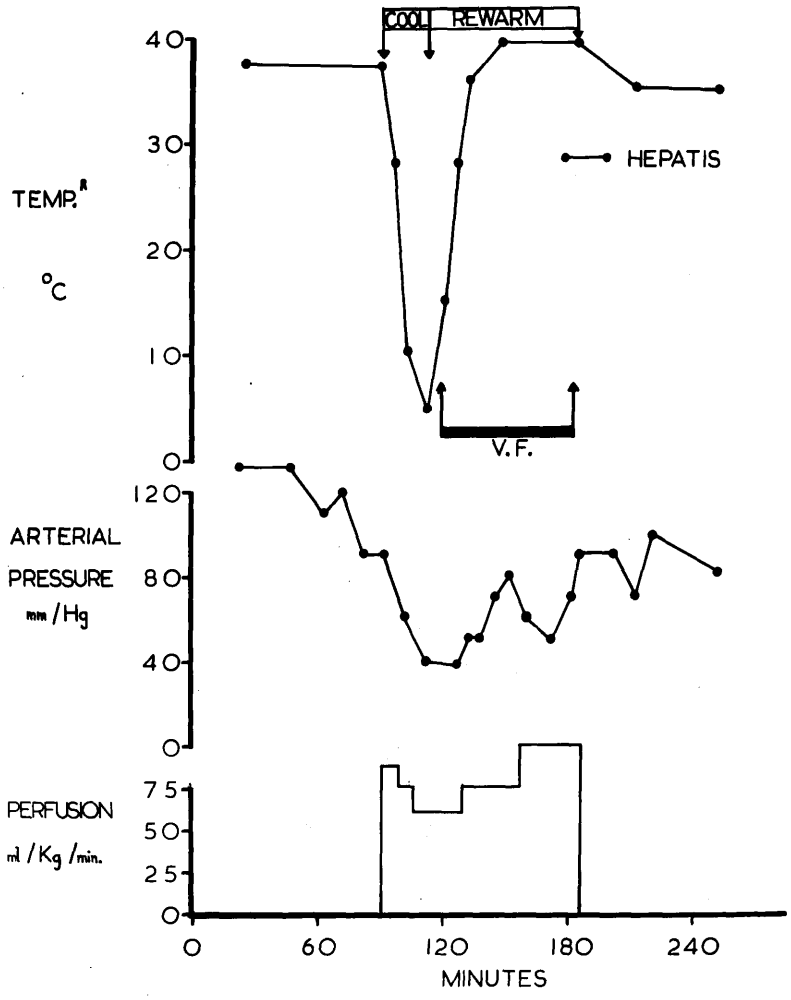
COOL
REWARM
HEPATIS
TEMP.R
°C
40
30
20
10
0
V.F.
120
ARTERIAL
PRESSURE
mm/Hg
80
40
0
75
PERFUSION
ml/Kg/min.
50
25
0
0
60
120
180
240
MINUTES

Figure 25.

During the immediate post-operative period the dog was laid on an electric blanket and warmed with the infra-red heater. An after-drop of 5°C. occurred in the porta hepatis temperature but no after-drop was observed in the rectal temperature. Subsequent recovery was relatively uneventful despite a drainage of 450 ml. of blood from the chest. A corresponding amount of donor blood was given intravenously to replace this loss. The animal regained consciousness when the rectal temperature was 36.4°C., 8 hours after completing the perfusion. The temperature subsequently rose to 38.8°C. after a further 6 hours, by which time he was fully awake and able to drink water. Chest drains were removed after 20 hours, and by the second day the dog was eating and drinking well and able to go for a short walk. He made a complete recovery and it is interesting to note that prior to the experiment he had been taught several parlour tricks, for which he retained full memory after the experimental procedure. This dog is alive and well at the time of writing.

EXPERIMENT 14 28.4.58.

A 10 kg. dog was anaesthetised and prepared as in the previous experiment. 10 mg. heparin per kilogram body weight were administered before commencing perfusion. Cooling to a porta hepatis temperature of 3.6°C. was achieved in 35 minutes, and rewarming to 40°C., with the assistance of the infra red heater, in 45 minutes. An after-drop in rectal temperature of 4.4°C. to 32.5°C. occurred over 2 hours; 6½ hours later it had risen to 38°C. The dog regained consciousness soon afterwards and the temperature continued to rise to 41°C. over a further 2½ hours. During this period there had been a loss of 400 ml. of blood from the chest drain and 500 ml. of blood were replaced intravenously. The animal made an uneventful recovery, and apart from weakness in the left foreleg and an elevated temperature for 4 days, appeared normal in every respect. He was observed for 8 weeks and then sacrificed.

EXPERIMENT 15 12.5.58.

An 11 kg. dog was anaesthetised and prepared in the same way as in the previous two experiments, with a similar dosage of heparin intravenously. Cooling to a porta hepatis temperature of 5°C. occurred in 22 minutes and rewarming, with the assistance of infra-red heaters, to 40°C. in 35 minutes. The perfusion was continued at this temperature for a further 5 minutes. Cardiac asystole of 22 minutes duration was observed between 13.5°C. on cooling and 15°C. on rewarming. An after-drop of 3.5°C. in rectal temperature occurred over 4 hours and thereafter rewarming to 38°C. took 5 hours. 275 ml. of blood were administered over this period to replace a loss of 150 ml. from the chest drain.

The dog made a satisfactory recovery and was observed for 7 weeks, then sacrificed.

EXPERIMENT 16 19.5.58.

A 10.5 kg. dog was anaesthetised and prepared for experiment as previously described. With perfusion and rapid cooling a porta hepatis temperature of 5°C. was reached in 19 minutes. Cardiac asystole occurred at 12.4°C. on cooling and continued for 19 minutes, until a temperature of 14.7°C. on rewarming. When the hepatic temperature was approximately 22°C. on rewarming, the coil of the heat exchanger ruptured with a considerable loss of blood into the coolant circuit. The inlet and outlet tubes were clamped, the heat exchanger stripped down and the tear in the membrane found. This had resulted from an excessive pressure in the apparatus, due to a constriction at the outlet connection caused by faulty assembly. The coil was replaced and the heat exchanger re-assembled. This took 20 minutes. During this period the dog's arterial pressure had fallen to 15 - 20 mm. Hg. and the temperature to 19.5°C. On re-commencing the perfusion, many air bubbles were noted in the bubble trap, some of which entered the arterial tubing. Rewarming was continued to 40°C. and the experiment completed in an attempt to survive the dog. After the usual after-drop in rectal temperature from 35.2°C. to 32.1°C., rewarming to 36.2°C. occurred over 4 hours. The dog did not show any attempt at spontaneous respiration, and suddenly collapsed and died 7 hours

after completing the experiment.

Post mortem showed areas of collapse in both lungs. The brain showed petechial haemorrhages but there was no macroscopic or microscopic evidence of emboli. Other organs were pale, but otherwise normal. Death was considered to be due to air embolism.

EXPERIMENT 17 20.5.58.

A 10 kg. dog was anaesthetised with intravenous sodium thiopentone and prepared for experiment as previously. The perfusion was commenced and the porta hepatis temperature reduced to 4.8°C. in 22 minutes. Rewarming to 40°C. occupied 42 minutes and this temperature was maintained for a further 5 minutes. Cardiac asystole, between 11.7°C. and 14.2°C., lasted for 19 minutes. On completing the perfusion, the rectal temperature fell from 35.3°C. to 30.5°C. over 1 hour 16 minutes. Rewarming to 38°C. occurred over the following 5 hours 30 minutes. Consciousness was regained at 35.5°C. 150 ml. of blood lost from the chest was replaced by 200 ml. of blood intravenously.

The dog made a complete recovery and behaved normally during 6 weeks' observation.

EXPERIMENT 18 21.5.58.

A 10 kg. dog was anaesthetised and the experiment performed as previously described. On cooling, a porta hepatis temperature of 4°C. was reached in 18 minutes and rewarming to 40°C. in a further 22 minutes, at which temperature the perfusion was continued for 5 minutes. Cardiac asystole of 20 minutes was observed between 13°C. on cooling and 16.4°C. on rewarming. Rectal temperature on completing the perfusion was 31°C. and there was no after-drop of this temperature. Rewarming to 38°C. occurred in 3 hours 30 minutes and the dog regained consciousness one hour later, when the temperature was 39.5°C. 150 ml. of blood drained from the chest during this period and was replaced by 200 ml. intravenously. However, about an hour later the dog suddenly collapsed and the rectal temperature fell 1°C. within 30 minutes. 200 ml. of blood and 50 ml. 1/200,000 noradrenaline were infused intravenously and the dog recovered and rewarmed to 39.6°C. Further recovery and convalescence were uneventful and he was walking and eating by the following evening. He was observed for 6 weeks and appeared perfectly normal in all respects.

EXPERIMENT 19 22.5.58.

An 11 kg. bitch was anaesthetised and prepared as in previous experiments. A porta hepatis temperature of 4°C. was reached in 16 minutes and rewarming to 40°C. in 32 minutes. The perfusion was continued at this temperature for a further 5 minutes. Cardiac asystole of 18 minutes occurred between temperatures of 14°C. on cooling and 13.8°C. on rewarming. On completing the perfusion the rectal temperature was 29°C. and no after-drop occurred. This rose to 34.6°C. over 4 hours 23 minutes, when the animal suddenly collapsed and died. During the rewarming period 250 ml. of blood drained from the chest and was replaced with 120 ml. donor blood, no more being available.

At post mortem there were a further 200 ml. of blood in the chest, with patchy collapse of the lungs. All organs were pale, but otherwise appeared normal.

Observations

1. Death was caused by haemorrhage.

2. This experiment emphasized the need for adequate replacement of blood during the post-operative period.

EXPERIMENT 20 23.5.58.

A 10.5 kg. bitch was anaesthetised and prepared as previously described. On cooling a porta hepatis temperature of 4.6°C. was reached in 21 minutes and rewarming was completed in 53 minutes. Cardiac asystole of 14 minutes was observed from 14.4°C. on cooling to 13.2°C. on rewarming. On completing the experiment the rectal temperature was 31.5°C. and no after-drop occurred. Rewarming to 38.5°C. occupied 5 hours, by which time the animal regained consciousness. 180 ml. of blood drained from the chest and was replaced by 180 ml. intravenously. She made an uneventful recovery and was able to walk, eat and drink 18 hours after completing the experiment. Seven weeks later she gave birth to a litter of four normal puppies, having been pregnant for a period of approximately 14 days prior to the experiment.

CHAPTER V

DEEP HYPOTHERMIA WITH TOTAL CIRCULATORY ARREST.

ACUTE EXPERIMENTS

Six experiments were performed. In the first three, the small oxygenator and simple cooling coil primed with dextran were used; in experiments 4 and 5 the Mark I heat exchanger was incorporated in the perfusion circuit with donor dog blood for priming and in the final experiment the Mark II heat exchanger replaced the Mark I. Experiments 1 to 3 were performed simultaneously with the acute experiments described in Chapter III and the final three with the survival series described in Chapter IV.

EXPERIMENT 1 8.6.57.

A 14 kg. dog was anaesthetised with intravenous sodium thiopentone and respiration maintained on the respiratory pump, using air to ventilate the lungs. A femoral vein was cannulated for intravenous medication and the upper mediastinum exposed through a 3rd space transverse thoracotomy. The left subclavian artery and venae cavae were prepared for cannulation as previously described and the vena azygos ligated. 5 mg. heparin per kilogram body weight were given intravenously and the femoral artery cannulated for arterial pressure recording. Mercury-glass thermometers secured in the porta hepatis, rectum and adductor muscle of thigh were used for temperature observation. The perfusion circuit, consisting of the pump, with small oxygenator, simple cooling coil and bubble trap, was primed with dextran. The subclavian artery and superior and inferior venae cavae were cannulated, bubbles excluded and the circuit completed.

On cooling, the porta hepatis temperature was reduced from an initial 36.5°C. to 3.7°C. in 140 minutes. Cardiac arrest occurred at 8.5°C. when pulmonary ventilation was discontinued. On reading 3.7°C. the perfusion was stopped and the dog was then left without corporeal or extra-corporeal circulation for 30 minutes. During this period the porta hepatis temperature rose slowly to 6.2°C. The perfusion was then resumed and the

heat exchanger rewarmed. Ventricular fibrillation was noted on the E.C.G. when the porta hepatis temperature reached 22.2°C. An attempt was made to convert the fibrillation by recooling but during this period pulmonary oedema developed and the experiment was abandoned.

Observations

1. Apart from the 30 minute circulatory arrest there was no obvious cause for the ventricular fibrillation. A total of 80 ml. of normal saline had been infused during the experiment.

2. At one point, the level of the blood in the oxygenator was low and it is possible that coronary air embolus occurred during this period. However, no alteration was noted in the level of the bubble trap.

3. When the perfusion was recommenced after the 30 minutes arrest, the venous catheter blood was dark in colour, in marked contrast to the minimal arterio-venous difference noted at low temperatures in the previous experiments. This would indicate that oxygen was still being utilized by the animal.

EXPERIMENT 2 13.6.57

A 17 kg. dog was anaesthetised with intravenous sodium thiopentone and both preparation and apparatus used, were identical to the previous experiment. 5 mg. of heparin per kilogram body weight were administered prior to cannulation. The porta hepatis temperature was reduced from 36.3°C. to 4.8°C. in 72 minutes, and at this point all circulation was discontinued for 20 minutes. During cooling, the heart fibrillated for 5 minutes between 13.2°C. and 11.8°C. when it reverted to normal rhythm for a few beats, after which action ceased altogether. Pulmonary ventilation was discontinued at this point. During the period of total circulatory arrest, the dog appeared very dead indeed, with widely dilated pupils and dilated venules in the tongue. The limb muscles were firm and cold, but there was no rigidity. No reflex activity could be elicited. During the 20 minute period arterial pressure remained at 10 mm. Hg. and the porta hepatis temperature rose to 6°C. Perfusion was restarted and gradual rewarming of the heat exchanger commenced immediately. Normal cardiac contractions commenced at 22.9°C. Rewarming was continued until 32.3°C. was reached, when the perfusion was discontinued. By this time the pupils had contracted and brisk tendon jerks could be elicited. When the catheters were removed the heart maintained an arterial pressure of 95 - 100 mm. Hg. during 60 minutes observation. The porta hepatis temperature

fell to 26°C. before the experiment was terminated. The temperatures, arterial pressure and perfusion rate are charted in Figure 26.

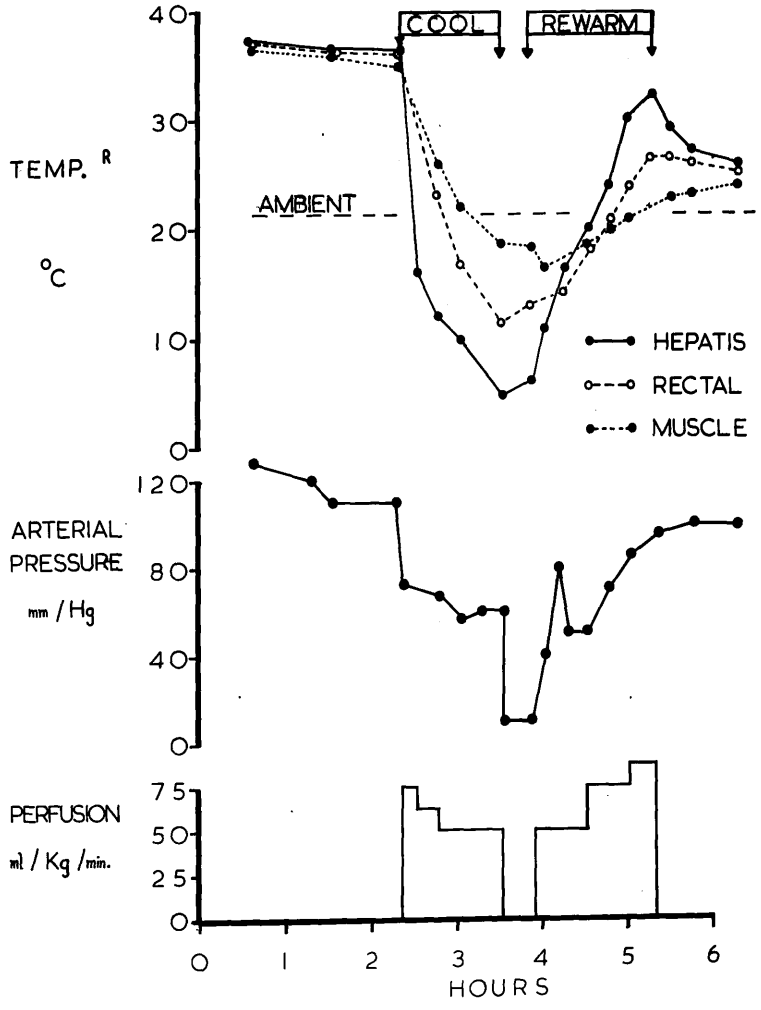

Figure 26. 20 minutes total circulatory arrest between cooling and rewarming.

Observations

1. As in the previous experiment reduction in oxygen content of the venous catheter blood was noted on recommencing the perfusion. This reverted to the usual oxygenated appearance after a few minutes' perfusion.

2. Normal cardiac action was restored after 20 minutes total circulatory arrest.

3. During the total circulatory arrest the porta hepatis and rectal temperatures rose, and that of the muscle fell.

EXPERIMENT 3 21.6.57.

A 14 kg. dog was anaesthetised by intravenous sodium thiopentone and the preparation and apparatus were identical to the two previous experiments. 5 mg. of heparin per kilogram body weight were administered prior to cannulation. On cooling the porta hepatis temperature was lowered from 36°C. to 5.4°C. in 85 minutes. Cardiac arrest occurred at 12°C., 45 minutes after cooling was commenced. Rectal and muscle temperatures were 8.9°C. and 12.7°C. respectively. The dog was packed in ice, the cannulae clamped and disconnected from the perfusion and recording apparatus and then placed in a refrigerator at +3°C. for 16 hours.

On removal there was rigidity of all body muscles including the tongue, the temperature of which was 4°C. and this was the maximum recorded in any part of the body. The pupils were widely dilated and the eyes glazed. The catheters were reconnected, rewarming commenced and resuscitation attempted. The circulation was restored and arterial pressure elevated to 40 mm. Hg. A blood flow was observed in the venules of the tongue and the retinal vessels, and the tongue muscle soon became flaccid. Pulmonary ventilation was commenced at 19°C. and the lungs expanded well. Rewarming was continued to 30.6°C. but there was no evidence of cardiac activity either by contraction

or on E.C.G.; the limb muscles did not relax from the state of rigor. The final rectal and muscle temperatures recorded were 23.9°C. and 15°C. respectively. 0.04 mg. of noradrenaline injected intravenously elevated the arterial pressure to 100 mm. Hg., but had no other apparent effect. The experiment was terminated at this point.

On subsequent examination, the main limb vessels were patent, but there was no evidence of peripheral flow or of the muscles having been oxygenated.

Observations

In view of subsequent experience, this experiment would appear to have been performed somewhat prematurely.

EXPERIMENT 4 11.9.57.

A 16 kg. dog was anaesthetised with intravenous sodium thiopentone and the preparation proceeded with as before. The Mark I heat exchanger was used, and the extra-corporeal circuit primed with donor dog blood. Porta hepatis and rectal temperatures were recorded. The dog was cooled to 6°C. in 42 minutes, cardiac asystole occurring at 13.1°C. The perfusion was then discontinued for 20 minutes, during which time the porta hepatis temperature increased to 8.9°C. and the rectal temperature from 10.2°C. to 13.8°C. At this point slow ventricular fibrillation was noted on the E.C.G. and on inspecting the heart this was confirmed. The perfusion was restarted and the venous blood was noted to be very reduced. Recooling to a porta hepatis temperature of 5.9°C. and subsequent rewarming failed to convert the fibrillation. Further attempts at conversion were made with 2 ml. of 25 per cent potassium citrate, injected into the aorta, on two occasions when the temperature had reached 30.5°C. and 31°C. Both were unsuccessful and the experiment was abandoned.

Observations

1. Ventricular fibrillation occurred after 20 minutes total circulatory arrest and could not be reversed by recooling or potassium citrate.

2. Marked reduction in oxygenation of venous blood was again noted following the period of arrest.

3. Relatively high arterial pressure during the period of circulatory arrest and presumably high venous and capillary pressure, may have contributed to myocardial damage.

EXPERIMENT 5 21.11.57.

The experiment was repeated on an 11 kg. dog using the same preparation and apparatus. Thermocouples were placed in the porta hepatis, rectum, adductor muscle of thigh, neck muscle, shoulder muscle and within the pericardium. Blood samples were removed at intervals for plasma sodium, potassium, osmolarity, haemoglobin and fibrinogen content. Whole blood haemoglobin and arterial and venous oxygen saturation were also estimated. Stained slides were examined for platelets and white blood cells.

5 mg. heparin per kilogram body weight were administered intravenously before cannulating the vessels. On cooling the porta hepatis temperature was lowered to 13°C. and the heat exchanger then stabilised at 15°C. for 15 minutes, after which the blood samples were taken, the porta hepatis temperature now being 15.5°C. Cardiac arrest occurred at 12.8°C. during the second phase of cooling. Cooling was then continued to 5°C. when the perfusion was discontinued for 60 minutes. The total time required to reach this temperature was 90 minutes. During the period of circulatory arrest the arterial and venous catheters were unclamped and the blood from the dog allowed to drain into the oxygenator where it was slowly circulated and the heat exchanger temperature held at 5°C. Iced saline

was placed into the thoracic cavities to maintain a low cardiac temperature. After 60 minutes the heart was only slightly distended and the muscle flaccid. The saline was then sucked from the chest and perfusion and rewarming commenced. The first flush of venous blood was very dark, but soon regained its usual oxygenated appearance. Ventricular fibrillation was noted at 18.5°C. and continued throughout rewarming; when the porta hepatis temperature reached 30°C. it was converted to sinus rhythm with 1 ml. of 25 per cent potassium citrate, injected into the aorta, but fibrillation resumed within 4 minutes. Further attempts at conversion were unsuccessful and the experiment was abandoned. 56 minutes were required for the whole rewarming period.

Temperature records are reproduced in Figure 27 and blood changes are plotted against temperature in Figure 28.

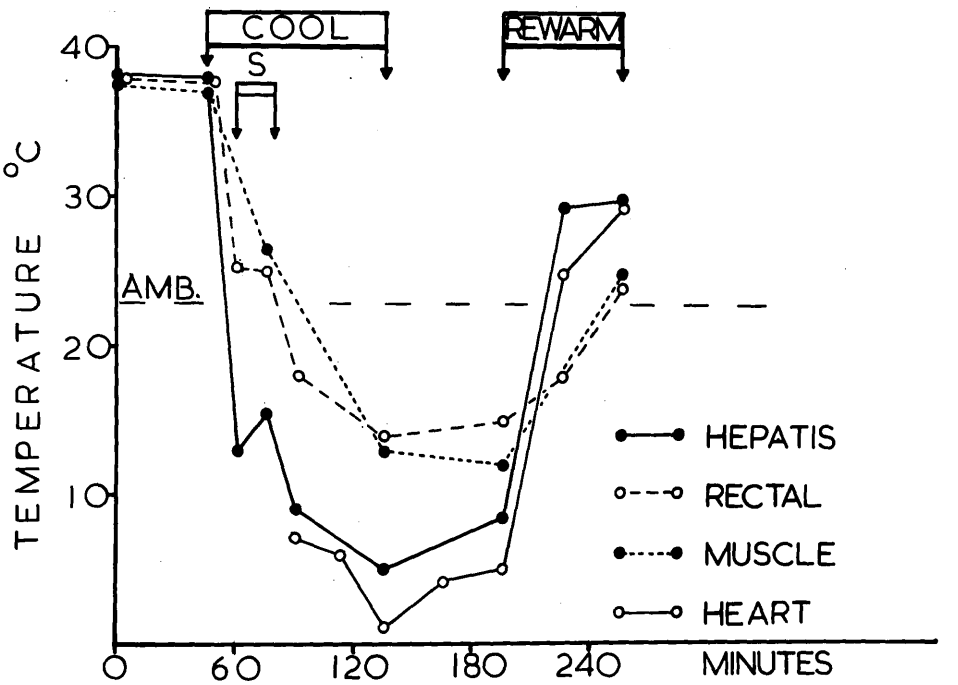

Figure 27. Neck muscle temperature is charted.

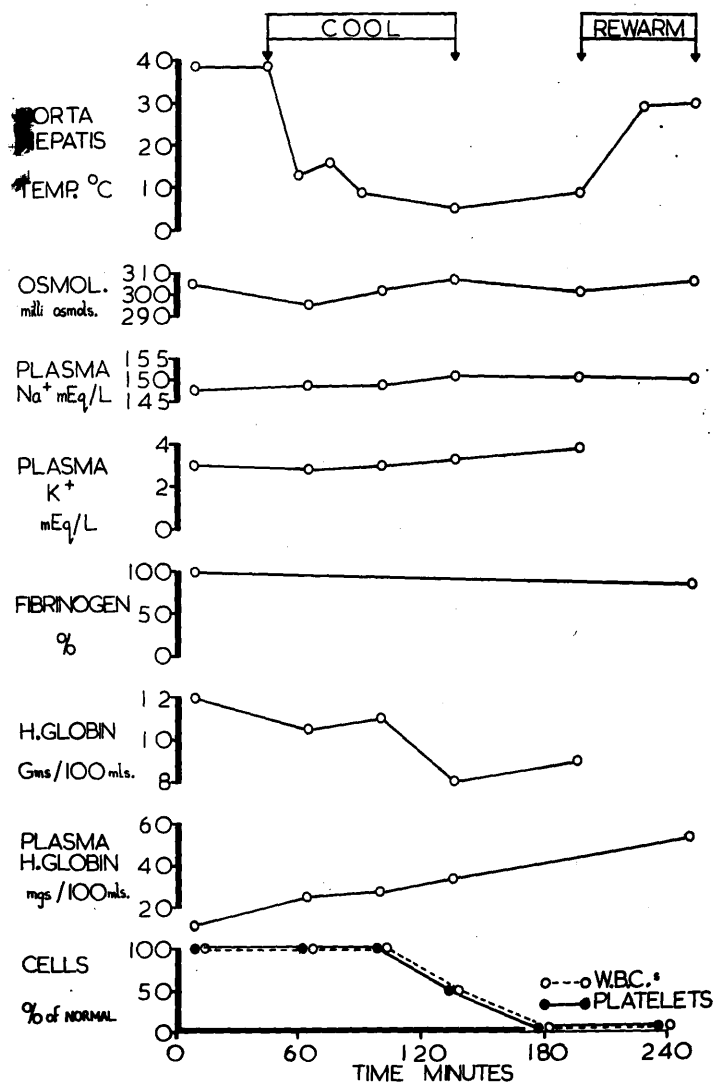
COOL
REWARM
PORTA HEPATIS TEMP. °C
40
30
20
10
0
OSMOL. milli osmols.
310
300
290
PLASMA Na+ mEq/L
155
150
145
PLASMA K+ mEq/L
4
2
0
FIBRINOGEN %
100
50
0
H.GLOBIN Gms/100 mls.
12
10
8
PLASMA H.GLOBIN mgs/100mls.
60
40
20
CELLS % of NORMAL
100
50
0
W.B.C.'s
PLATELETS
0
60
120
180
240
TIME MINUTES

Figure 28.

Observations

1. Ventricular fibrillation occurring after the circulatory arrest was not influenced by cardiac cooling, or by lowered arterial pressure during circulatory arrest.

2. The oxygenator was relatively inefficient even with the small experimental animal used.

3. Fibrinogen content of plasma was satisfactory after 146 minutes perfusion, but platelets and white blood cells were much reduced.

4. Hind limb and neck muscle temperatures did not vary by more than $\pm$ 0.5°C. during the experiment. Fore limb muscle temperature was 5°C. lower than that of the neck during the period of circulatory arrest.

EXPERIMENT 6 19.12.57.

The experiment was repeated on a 10.5 kg. dog, with the Mark II heat exchanger incorporated in the perfusion circuit. 10 mg. heparin per kilogram body weight were used in this experiment before inserting the cannulae. The porta hepatis and rectal temperatures were recorded; also those in the muscles of a hind limb and the neck. Five blood samples were taken during the experiment for white cell and platelet estimation. The dog was cooled to 3.7°C. in 45 minutes without any temperature stabilisation. Cardiac arrest occurred at 6.3°C. The perfusion was discontinued for 60 minutes and the thoracic cavity maintained at 0°C. with iced saline as in the previous experiment; at the end of this period the porta hepatis temperature had risen to 8°C.

When the perfusion was recommenced, the heat exchanger was maintained at 0°C. for 15 minutes before rewarming rapidly. Ventricular fibrillation was observed at a porta hepatis temperature of 17.5°C. Rewarming to 35°C. was completed in 56 minutes which included the 15 minutes of cooling referred to above. The heart was then successfully defibrillated with 2 ml. of 25 per cent potassium citrate injected into the ascending aorta and maintained a mean arterial pressure of 70 mm. Hg. during 60 minutes observation, without assistance

from the extra-corporeal circulation.

Observations

1. Ventricular fibrillation was successfully converted and satisfactory cardiac action obtained after 60 minutes total circulatory arrest.

2. Using 10 mg. of heparin per kilogram body weight resulted in a normal number of platelets and white blood cells after a perfusion of 95 minutes.

3. The muscle temperatures closely followed each other as in the previous experiment, both falling to 14.5°C. on cooling and rising to 16.5°C. (leg) and 17.3°C. (neck), after 60 minutes of total circulatory arrest. The ambient temperature was 22.5°C. during this period.

CHAPTER VI

DEEP HYPOTHERMIA WITH CIRCULATORY ARREST AND EXSANGUINATION.

SURVIVAL EXPERIMENTS

PART I

Twenty-three experiments were performed in this series. In all experiments the large oxygenator and Mark II heat exchanger were primed with donor dog blood. In the first six a transverse thoracotomy and subclavian cannulation combined with 10 mg. heparin per kilogram body weight were used. For subsequent experiments a right 4th space thoracotomy and iliac arterial cannulation were combined with 5 mg. heparin per kilogram body weight. In experiments 10 to 22 the muscles were pre-cooled with ice prior to perfusion.

EXPERIMENT 1 30.7.58.

A 10 kg. dog was anaesthetised with intravenous sodium thiopentone, intubated and respiration maintained with a 50:50 nitrous oxide, oxygen mixture delivered by the respiratory apparatus. The left femoral vein was cannulated and a slow 5 per cent dextrose infusion used as a vehicle for further thiopentone or pethidine. The upper mediastinum was exposed through the 3rd interspace after the method of Andreason and Watson (1953) and the left subclavian artery and atrium prepared for cannulation as previously described. Thermocouples were placed in the porta hepatis, rectum and adductor muscle of thigh. After the administration of 10 mg. heparin per kilogram body weight, the left femoral artery was cannulated for blood pressure recording and the left subclavian artery and venae cavae cannulated as in previous experiments. The perfusion apparatus with the large oxygenator and Mark II heat exchanger, was primed with donor dog blood and when the circuit was completed and bubbles excluded from the arterial and venous tubes, the perfusion was commenced.

The dog was cooled to a porta hepatis temperature of 3.6°C. in 26 minutes. Cardiac arrest occurred at 9°C. The perfusion was discontinued for 30 minutes. Blood was allowed to syphon from the cavae and aorta into the oxygenator during this time.

On resuming the perfusion the porta hepatis temperature had risen to 7.2°C., but 3 minutes of recooling reduced this to 6.8°C. Rapid rewarming was then instituted and normal cardiac action commenced at 12°C. Rewarming to 40°C. and maintenance of this temperature for 5 minutes with the assistance of the infra-red heaters as used in later survival experiments described in Chapter IV, was completed in 55 minutes. The perfusion was then discontinued.

Chest closure and drainage was completed, during which time the porta hepatis temperature fell to 32.4°C. The rectal temperature at this time was also 32.4°C. The dog then started to rewarm. Spontaneous respiration was observed at 34°C.; the pupils were contracted and there was an active corneal reflex. Further rewarming to 39.4°C. occurred six hours after completing the perfusion and over the following 5 hours 30 minutes the temperature slowly fell to 38.2°C. 100 ml. of blood drained from the chest and was replaced by 150 ml. intravenously. Urine was passed on two occasions and pulmonary ventilation was satisfactory.

11 hours 45 minutes after completing the perfusion the dog suddenly collapsed and died. Artificial respiration, infusion of blood and noradrenaline failed to resuscitate the animal. The haematocrit at this time was 38 per cent.

Post mortem examination showed no evidence of haemorrhage. The heart, lungs and brain were normal; other organs were also normal.

Observations.

1. The dog breathed spontaneously and showed normal cough and pupillary reflexes. It did not recover consciousness.

2. The immediate cause of death was apparently due to cardiac failure. There was no evidence of anaemia or oligaemia to precipitate this.

EXPERIMENTS 2 11.8.58.
3 18.8.58.

These experiments were performed on 12 and 13.5 kg. dogs using an identical technique to that described in experiment 1. Heparin, 10 mg. per kilogram body weight, was administered prior to cannulation, and the porta hepatis, rectal and adductor muscle temperatures were recorded. In addition, arterial blood samples were removed before commencing and after completing the perfusion for the estimation of plasma serotonin (5-hydroxytryptamine).

The dogs were cooled to porta hepatis temperatures of 4.8°C. and 4.2°C. in 28 and 33 minutes respectively. In both experiments a period of 30 minutes total circulatory arrest was observed and was then followed by rapid rewarming to 40°C.; this temperature was maintained for 15 minutes before discontinuing the perfusion. This period occupied 60 minutes in experiment 2 and 72 minutes in experiment 3. Normal cardiac action was restored in each case. An after-drop of the porta hepatis temperature occurred in each dog to 32.8°C. and 33.5°C. to be followed by a slow rise in the rectal temperature to 38°C. and 39.5°C. respectively. Dog 2 died after 4 hours 30 minutes and dog 3 after 6 hours.

At post mortem in both cases there were small areas of collapse in the lungs, but the other organs appeared normal.

The arterial blood samples were centrifuged immediately

after collection, the supernatant plasma separated and stored at -20°C. When subsequently analysed for serotonin (5-hydroxytryptamine) content not one of the four samples showed any appreciable activity.

Observations

These experiments were performed on the assumption that damage to the blood cells, particularly the platelets, during the perfusion might release serotonin, with a rise in the plasma values. This hypothesis was not confirmed.

EXPERIMENT 4 20.8.58.

The experiment was repeated on a 10.5 kg. dog, with the addition of a burr hole in the temporal region of the skull and a thermocouple placed to lie outside the dura, over the cerebral cortex. Electro encephalogram leads were attached to the skull and to the E.E.G. apparatus, which was monitored by an oscilloscope. 10 mg.heparin per kilogram body weight were administered prior to catheterisation and porta hepatis, muscle, rectal and frontal sinus temperatures were recorded, in addition to that of the brain. The dog was cooled from a porta hepatis temperature of 37.4°C. to 3.4°C. in 29 minutes. The E.E.G. waves were minimal at a brain temperature of 23.4°C. and disappeared at 21°C. Cardiac arrest occurred at 13.5°C. When the porta hepatis temperature was 3.4°C. the corresponding brain temperature was 10°C. Ice packs were placed on the head during the 30 minutes total circulatory arrest with exsanguination and hepatic and brain temperatures rose to 7.2°C. and 13.5°C. respectively, by the end of this period. The perfusion was then resumed and the dog recooled for 10 minutes. The ice packs were removed and rewarming and infra-red heating commenced. Heart action was restored at a porta hepatis temperature of 16.8°C. and E.E.G. waves were noted at 21.2°C.(brain temperature) when the porta hepatis had risen to 21°C. Rewarming to 40°C.

was completed in 47 minutes, when the perfusion was discontinued. The after-drop occurred over 40 minutes, and the porta hepatis and brain temperatures both fell to 33.6°C. The temperatures during and immediately after perfusion are recorded in Figure 29 and a photographic recording of the E.E.G. during perfusion in Figure 30.

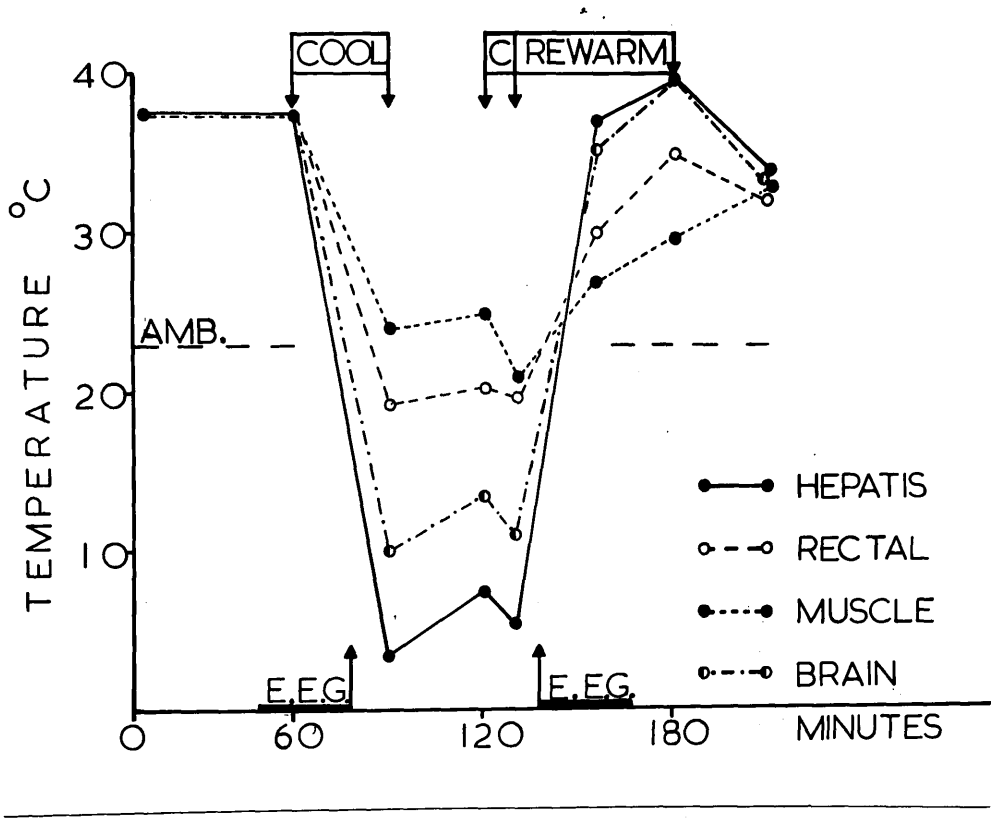

Figure 29. Perfusion discontinued between cool and rewarm. At C, temporary recooling was induced.

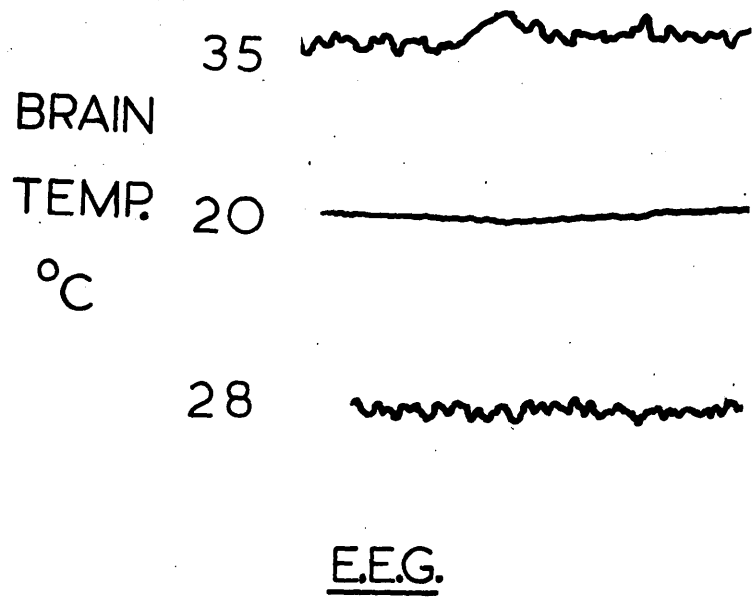

Figure 30

The dog subsequently rewarmed to 38.8°C. rectal temperature 5 hours 45 minutes after discontinuing the perfusion, by which time normal E.E.G. waves were observed. The temperature continued to rise to 40.4°C. over the following 2 hours 30 minutes, but although corneal reflexes were brisk the dog did not regain consciousness and it suddenly collapsed and died 10 minutes later. Chest drainage over this period totalled 150 ml. of blood and

230 ml. were replaced intravenously.

At post mortem there was no evidence of any bleeding points and all ligatures were intact. The heart, brain and other organs appeared normal.

Observations.

1. The dog did not regain consciousness despite normal E.E.G. appearances.

2. Brain temperatures appeared to be maintained at a satisfactory level during the circulatory arrest, and no E.E.G. activity was noted.

3. The frontal sinus and brain temperatures bore a close relationship to each other below 20°C; the variation did not exceed ± 1°C.

EXPERIMENT 5 25.8.58.

A 10 kg. dog was anaesthetised and the preparation conducted as in previous experiments. A burr hole was made in the right temporal region and a thermocouple placed extra-durally as in the last experiment. In addition to brain temperatures, temperatures of the porta hepatis, rectum and adductor muscle of thigh were recorded. The electro encephalogram was also observed during the experiment. The dog was cooled from a porta hepatis temperature of 36°C. to 4.2°C. in 56 minutes, when the corresponding brain temperature fell to 4.4°C. E.E.G. waves disappeared at a brain temperature of 19.8°C. and cardiac contraction also ceased at 19.8°C. When the porta hepatis temperature of 10.8°C. was reached the dog was perfused with Ringer solution at 0°C. and the corporeal blood washed out to reduce the haematocrit to the region of 0.5 per cent. Cooling was then continued with the Ringer perfusion to 4.2°C., when the perfusion was discontinued. The skull was packed in ice and the dog was left in this state for 31 minutes. The apparatus was then reprimed with fresh donor dog blood containing sodium 152.2 mEq/litre and potassium 2.3 mEq/litre and on recommencing the perfusion, a 10 minute period of further cooling preceded rewarming. Normal cardiac contractions were observed at 11°C. and were well established at 16°C. Distinct E.E.G. waves

reappeared at 24.8°C. when the brain temperature was 20.6°C. Rewarming to 40°C. was completed in 107 minutes and the perfusion was then discontinued. The pupils which were widely dilated during the circulatory arrest, began to contract several minutes before discontinuing the perfusion. Temperature records during the experiment are shown below (Figure 31).

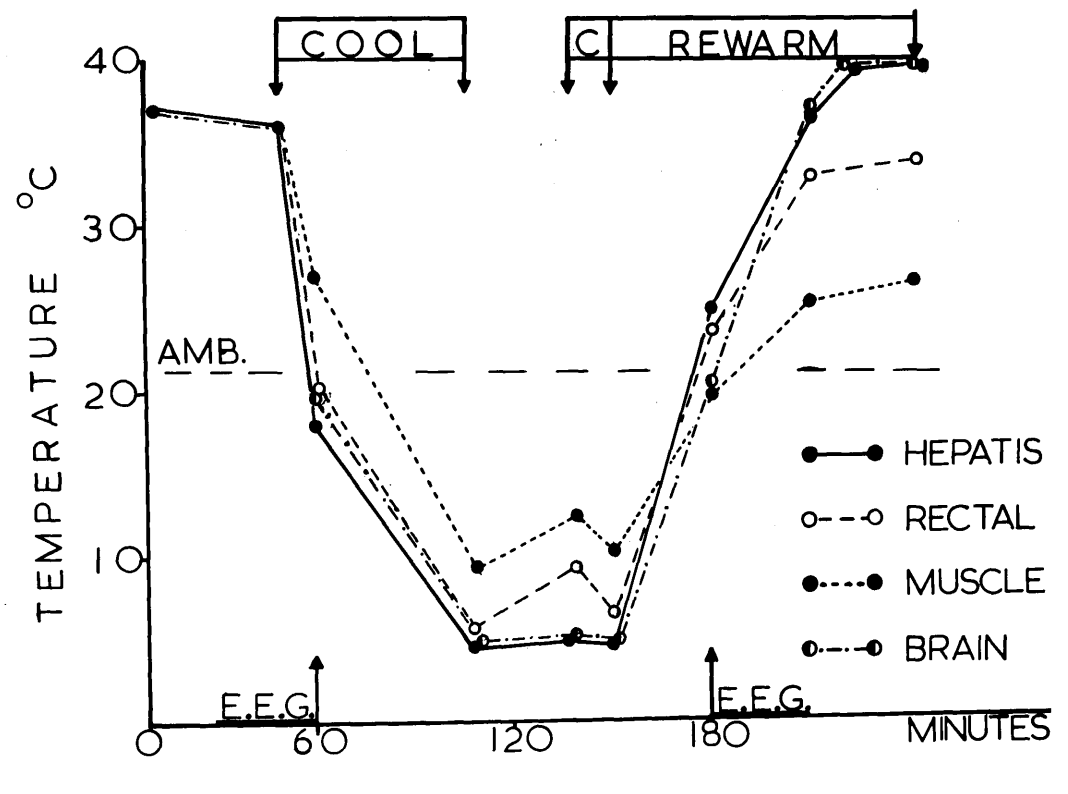

Figure 31. Circulatory arrest of 31 minutes between cool and rewarm. At C, the temporary recooling was induced.

All wounds were closed and the chest drained by which time the temperature fell to 34°C. The corresponding rectal temperature was 32°C., 35 minutes after completing the perfusion. The dog rewarmed to a rectal temperature of 35.6°C. 4 hours later. A temporal haematoma required aspiration at this time. Further rewarming did not occur and the dog died two hours later. 250 ml. of blood had drained from the chest and were replaced by 340 ml. of blood intravenously.

At post mortem there was a large subtemporal and a small extradural haematoma. There was no free blood in the chest, but there were small areas of collapse of the lungs. Apart from a flaccid distension of stomach and intestines, the organs appeared normal.

Observations

1. The experiment was performed on the assumption that during total circulatory arrest, red blood cells might sequestrate in the capillaries, particularly those of the brain, with resultant micro emboli.

2. Brain temperatures and E.E.G. changes closely followed those observed in the previous experiment.

3. The extradural haematoma may have been a contributory cause of death.

EXPERIMENT 6 8.9.58.

A similar procedure to that described in experiment 5 was performed on a 12 kg. dog with the exception of the temporal burr hole and brain thermocouple. A frontal sinus thermocouple gave approximate index of brain temperature. The dog was cooled from a porta hepatis temperature of 37.2°C. to 6.4°C. in 48 minutes. E.E.G. waves were much diminished when the sinus temperature reached 27°C. and disappeared at 24.2°C. Heart action ceased at a porta hepatis temperature of 15.8°C. When the temperature reached 9.2°C. replacement with Ringer solution commenced and cooling was continued to 6.4°C.; the perfusion was then discontinued for 30 minutes. The temperature rose to 9.6°C. and the dog was then recooled to 8°C. over the next 12 minutes. The Ringer solution was replaced with fresh donor dog blood during this period. Rewarming then commenced and cardiac systole was noted at 16°C. Ventricular fibrillation occurred at 22°C., with a spontaneous conversion at 23°C. E.E.G. waves were noted at 25°C. when the sinus temperature was 22.6°C. Rewarming to 40°C. was completed in 82 minutes. An after-drop to 35.6°C. occurred over 10 minutes and the rectal temperature which was then 28°C. slowly rose to 36.8°C. over the following 4 hours. Spontaneous respiration occurred at 31°C. Chest drainage totalled 340 ml. and was replaced by

500 ml. of blood intravenously. Four hours after completing the perfusion the dog suddenly vomited large quantities of bile stained gastric juice, some of which was inhaled. After aspiration of the vomitus from the lungs and aspiration of the stomach, the arterial pressure was restored from 70 mm. to 110 mm. and the dog appeared well. 45 minutes later it suddenly collapsed and died. A large quantity of urine had been voided prior to the initial collapse and a specimen of this contained 102.5 mEq/litre of sodium and 56 mEq/litre of potassium.

At post mortem the chest contained 300 ml. of clotted blood and the left lung was almost completely collapsed. The stomach was empty and there was no intestinal distension. Other organs, including the brain, appeared normal. The bladder contained approximately 50 ml. of urine and on analysis the sodium was 74 mEq/litre and potassium 84 mEq/litre.

Observations.

1. The gastric transudate most probably occurred during the replacement of the blood volume with Ringer solution and the consequent absence of the osmotic pressure of the plasma proteins. This was not recognised until lightening of the anaesthesia precipitated regurgitation.

2. Temporary ventricular fibrillation was again noted and although it converted spontaneously, this now suggested

inadequate coronary perfusion. It was possible that minor movements of the catheter, particularly when expanding the lungs after the circulatory arrest, might direct the jet of blood into the descending aorta, causing an ejector effect and inadequate perfusion pressure of the aortic arch.

3. Urinary elimination of sodium and concentration of potassium suggested satisfactory renal function.

EXPERIMENT 7 1.12.58.

This experiment was conducted on the assumption that in previous experiments gas micro emboli might have been produced in the tissues due to the wide temperature gradient between the perfused blood and the temperature of the experimental animal.

A 10 kg. dog was anaesthetised and respired as in previous experiments. The heart was exposed through a right 4th space thoracotomy and the right iliac artery through a right, oblique muscle splitting, lower abdominal incision. 5 mg. heparin per kilogram body weight was administered and the venae cavae cannulated as in previous experiments. The right iliac artery was cannulated and the tip of the cannula placed in the abdominal aorta mid way between the renal vessels and the trifurcation. Porta hepatis, rectal and muscle temperatures were recorded.

On cooling a gradient of not more than 10°C. was strictly maintained between the porta hepatis and the heat exchanger temperatures. Cooling to 4.3°C. occupied 51 minutes, E.E.G. activity ceased at 20.5°C. and cardiac asystole occurred at 13.5°C. On discontinuing the perfusion the dog was exsanguinated but the residual blood volume was not washed out as in experiments 5 and 6. After a period of total circulatory arrest of 30 minutes, the dog was briefly re-cooled for 3 minutes before rewarming commenced. During the rewarming a similar

gradient of temperature not exceeding 10°C. was observed between heat exchanger and porta hepatis. Rewarming to 40°C. was accomplished in 49 minutes and cardiac systole commenced at 16°C. and E.E.G. at 23°C. 150 ml. of blood had drained from the chest and was replaced by 300 ml. intravenously.

The dog survived the experiment for 5 hours and died suddenly when the rectal temperature was 35.5°C. Death was apparently due to cardiovascular collapse. At post mortem there were 150 ml. of blood in the chest and small areas of collapse of the upper lobe of the right lung. The heart, brain and other organs appeared normal.

EXPERIMENT 8 8.12.58.

The experiment was repeated on a 14.5 kg. dog, using an identical technique to that described in experiment 7. A porta hepatis temperature of 3.6°C. was reached in 42 minutes and following 30 minutes circulatory arrest and exsanguination, rewarming to 40°C. occurred in 71 minutes. E.E.G. activity disappeared at 18°C. on cooling and reappeared at 22.5°C. on rewarming. Cardiac asystole occurred between 13.8°C. and 14.7°C. The dog died suddenly 1 hour after completing the perfusion when the porta hepatis temperature had fallen to 35°C.

Arterial blood samples taken immediately after perfusion and immediately post mortem, yielded the following results when analysed:

	Post Perfusion	Post Mortem
Na mEq/litre	150	162
K mEq/litre	2.8	4.3
tCO_2 m/mols/litre	8.0	7.0

Observations

1. The tCO_2 values obtained indicated a gross acidosis. This appeared to be metabolic in origin, when considered with the pattern of death in this and previous experiments.

2. This acidosis had not been noted in previous survival experiments when there was no period of circulatory arrest.

3. Continued metabolism in muscle during the period of

circulatory arrest was the most likely source of acidosis. The muscle temperature had been relatively high in the majority of survival experiments with circulatory arrest completed to date. Possible exceptions occurred in experiments 5 and 6 where lower temperatures were noted as a result of the Ringer perfusion.

4. There was no evidence to suggest air emboli in either experiments 5 or 6, or that slow cooling and rewarming offered any advantages over the methods previously used.

EXPERIMENT 9 29.12.58.

An 11 kg. dog was anaesthetised with sodium thiopentone and prepared for experiment as previously described. The right thoracotomy and oblique abdominal incisions were used for cannulation of the venae cavae and iliac artery. Porta hepatis and rectal temperatures and E.E.G. were recorded and in addition frequent arterial blood samples were removed for estimations of pH, pCO_2, Na, K and haematocrit values.

The dog was rapidly cooled to 4.8°C. in 12 minutes, cardiac arrest occurring at approximately 18°C. Circulation was discontinued for 30 minutes and the dog exsanguinated into the oxygenator. The porta hepatis temperature rose to 12°C. towards the end of this period and on recommencing the perfusion, was recooled to 6°C. Slow rewarming was then commenced, observing a gradient of 5°C. between the heat exchanger and the porta hepatis temperatures. It took 64 minutes to raise the temperature to 40°C. and to maintain it at that level for 20 minutes. During rewarming an arterial pH of 7.08 was noted and 100 ml. of isotonic sodium bicarbonate (166 millimols/litre) solution were infused. On completing the perfusion there was a fall in porta hepatis temperature to 30°C.

In the post-experimental period the dog rewarmed very slowly to a rectal temperature of 36°C. in 5 hours. Pulmonary ventilation

was poor and there was considerable blood loss from all wounds. A total of 700 ml. of blood were transfused. 5 hours and 10 minutes after completing the perfusion it collapsed and died.

At post mortem there was no evidence of haemorrhage and all organs appeared macroscopically normal. Arterial pCO_2, pH, tCO_2, sodium and potassium are plotted against temperature in Figure 32.

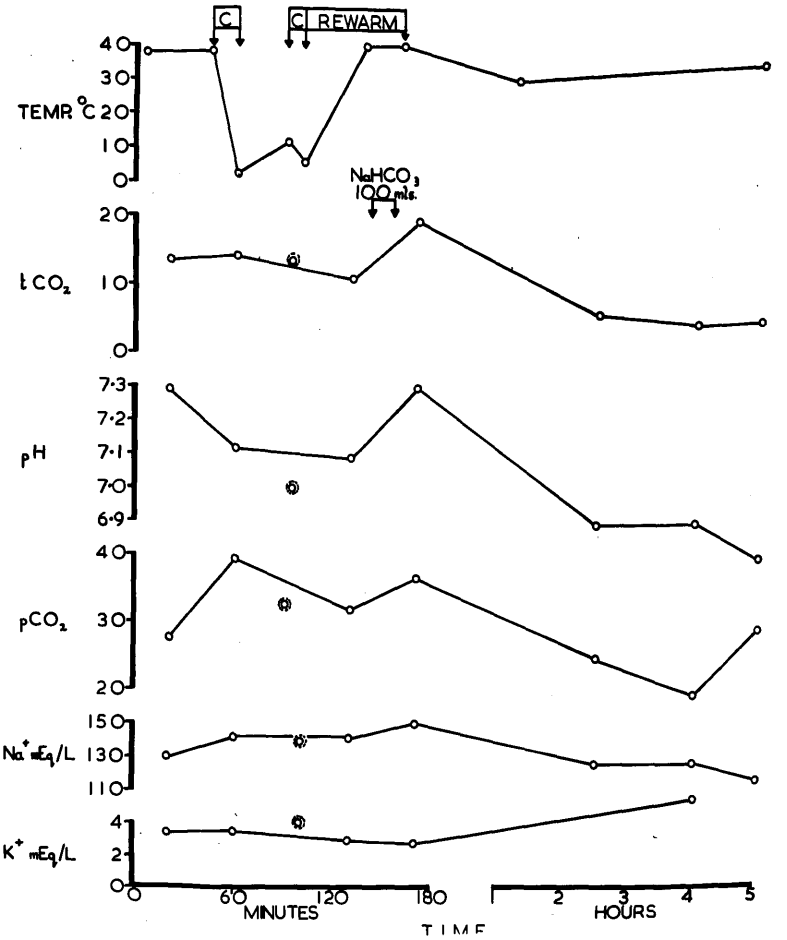

Figure 32. Perfusion discontinued for 30 minutes after cooling. At C, 10 minutes further cooling preceded rewarming.
pCO_2 mm. Hg.
tCO_2 millimols/litre.
⊙ venous catheter sample.

Observations

1. An increasing metabolic acidosis was noted during the experiment, which became very marked during the rewarming period. This was partially corrected by intravenous sodium bicarbonate, but the 100 ml. given was inadequate.

2. This would account for the delayed cardiac failure, central nervous depression and poor pulmonary ventilation noted in this and previous experiments.

3. The plasma potassium fell progressively during rewarming. A terminal rise may have been due to emergency transfusion of stored blood.

4. The fall in plasma sodium suggested over hydration during the post-operative period.

EXPERIMENT 10. 5.1.59.

A 13.5 kg. dog was anaesthetised with intravenous sodium thiopentone and the lungs ventilated as before. The subsequent procedure was identical to that of the preceding experiments. Porta hepatis, muscle and rectal temperatures were recorded but the E.E.G. was not observed. Arterial samples were removed for chemical analysis as in the previous experiment. Cooling from 37°C. to 3.6°C. was achieved in 41 minutes. Muscle temperature was then 20.6°C. During cooling 200 ml. of isotonic sodium bicarbonate solution were infused intravenously. A 30 minute period of circulatory arrest with exsanguination resulted in a rise of porta hepatis temperature to 6.8°C. and a further fall in muscle temperature to 16.8°C. Rewarming, assisted by infra-red heaters, occupied 70 minutes, the porta hepatis temperature being held at 40°C. for 32 minutes; the final muscle temperature was then 21.6°C. 250 ml. of sodium bicarbonate were infused during the rewarming stage. An after-drop in porta hepatis temperature to 32.5°C. was followed by rewarming to a rectal temperature of 38°C. 5 hours 40 minutes after completing the perfusion. Spontaneous respiration commenced at 33°C. and pulmonary ventilation improved during rewarming. The rectal temperature continued to rise to 39.9°C. when the dog suddenly collapsed and died 8 hours after completing

the experiment.

There had been steady oozing from the wounds during the post-operative stage but chest drainage did not exceed 150 ml. At post mortem there were 300 ml. of blood in the chest which had failed to drain and complete collapse of the right lung. Other organs were pale but otherwise normal. Temperature charts and metabolic results are shown in Figure 33.

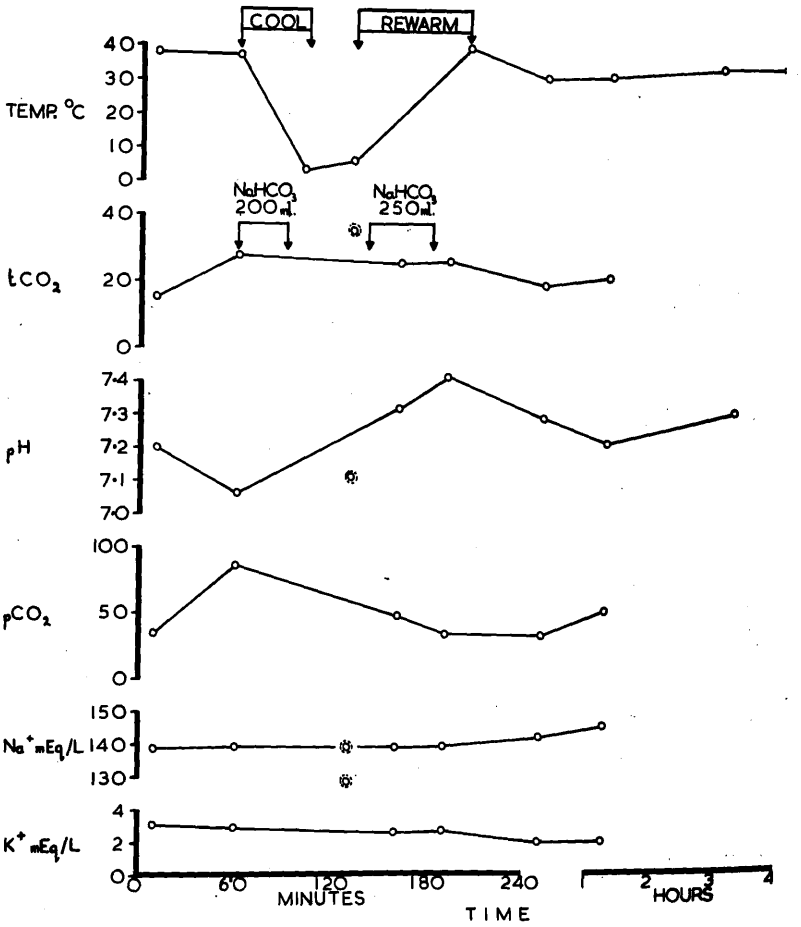

Figure 33. Perfusion discontinued for 30 minutes after cooling.
pCO_2 mm. Hg.
tCO_2 millimols/litre.
⊙ venous catheter sample.

Observations

1. The infusion of sodium bicarbonate had assisted in the control of the metabolic acidosis.

2. Failure of blood coagulation at normal temperatures was again noted. The haemothorax was not recognised during the post-operative period.

3. Both cooling and rewarming were rapid, but maintaining the temperature at 40°C. for 32 minutes, prolonged the total perfusion time to 111 minutes.

EXPERIMENT 11 12.1.59.

The experiment was repeated on a 12.5 kg. dog. The technique used was identical to that in the previous experiment, but additional arterial blood samples were removed to estimate coagulation times and blood films were made and stained with haematoxylin and eosin for platelets and white cell estimations.

The dog was cooled to a porta hepatis temperature of 4.8°C. in 52 minutes and during this period 200 ml. of isotonic sodium bicarbonate solution was infused intravenously. A period of 30 minutes circulatory arrest and exsanguination was followed by rapid rewarming. 40°C. was reached in 33 minutes and the temperature held at this point for a further 30 minutes. A further 250 ml. of isotonic sodium bicarbonate solution were infused during rewarming. An after-drop in porta hepatis temperature to 35.6°C. occurred, after which the rectal temperature, which was then 33.9°C., slowly rose to 38.7°C. over the following 6 hours. At this time the dog regained consciousness and was able to lap water. Pethidine mg. 25 was given intravenously to relieve pain. Considerable oozing from all wounds during this period and a drainage of 450 ml. of blood from the chest, were replaced by 625 ml. of blood intravenously. The coagulation time was 7 minutes and blood films showed only slight reduction in platelets and white blood cells. The dog

died suddenly 2 hours later when the rectal temperature was 39.5°C.

Observations.

1. The arterial pH had not fallen below 7.2 during the experiment or the recovery period. Half an hour before death it was 7.38.

2. The perfusion time of 115 minutes may have contributed to the prolonged coagulation time of the blood.

3. This was the first dog to regain consciousness in this series of experiments.

EXPERIMENT 12 6.2.59.

The experiment was repeated on a 12 kg. bitch using an identical technique to that in the previous experiments. The perfusion time, however, was reduced as much as was compatible with cooling to a sufficiently low temperature and rewarming to a safe temperature, before discontinuing the perfusion.

Cooling from a porta hepatis temperature of 35°C. to 6°C. was completed in 25 minutes, during which time 200 ml. of isotonic sodium bicarbonate were administered intravenously. After 30 minutes of total circulatory arrest, rapid rewarming was commenced and a porta hepatis temperature of 40°C. reached in 29 minutes and held at this point for 10 minutes. 275 ml. of sodium bicarbonate were given during rewarming and the lowest arterial pH recorded during the perfusion was 7.26. The porta hepatis temperature fell to 32.1°C. after 60 minutes, and the rectal temperature was then 31°C. The animal then rewarmed to 41°C. over the following 6 hours. Spontaneous respiration occurred at 34.2°C. and consciousness was regained at 37.5°C. which was approximately 4 hours 30 minutes after completing the perfusion.

The animal suddenly collapsed and died 7 hours 30 minutes after the experiment. At post mortem there were 600 ml. of blood in the peritoneal cavity. No source of haemorrhage was

detected, all ligatures on the iliac artery being intact; nor was there evidence of laceration of the liver which could have been caused by the tip of the thermocouple. There was partial collapse of the right lung but all other organs appeared normal.

PART II

A few alterations in procedure were made for the final group of eleven experiments. The experimental dogs were prepared with 0.125 mg. of digoxin given orally on the evening preceding the experiment. Aureomycin was given as previously described. During the experiment the period of stabilisation of arterial pressure before cooling was reduced to a minimum; cooling and rewarming times were completed as rapidly as possible using wide temperature gradients with the object of reducing the perfusion time to a minimum. Dogs were pre-cooled with ice to reduce the muscle temperature in experiments 13 to 22. Before removal of the vena caval catheters approximately 100 - 200 ml. of blood were bled from the dog into the oxygenator. The catheters were then clamped and a corresponding quantity of fresh donor dog blood, containing acid citrate dextrose solution as an anticoagulant, replaced intravenously. A solution of isotonic sodium bicarbonate, (166 mEq/litre), containing potassium chloride, 1.4 mEq/litre per kilogram weight of the experimental dog, and calcium gluconate, 40 ml. of 10 per cent solution per litre, was given intravenously during cooling and rewarming and as required during the post-experimental period. The rate of administration was monitored by the pH of the arterial blood measured at 37.5°C.

EXPERIMENT 13 9.2.59.

A 10 kg. dog was anaesthetised with intravenous sodium thiopentone and prepared as in the previous experiments. During this period ice was packed round the back and hind limbs. When the surgical procedures had been completed, the porta hepatis temperature had fallen to 32.4°C. One minute was required to stabilise the pump output and venous return, and cooling was then begun immediately. A porta hepatis temperature of 4.8°C. was reached in 18 minutes. Cardiac arrest had occurred at 12.5°C. All circulation was then discontinued and the dog exsanguinated. After 30 minutes rewarming commenced and a porta hepatis temperature of 40°C. was attained in 25 minutes and held at that point for a further 10 minutes, after which the perfusion was discontinued. Infra red heating was also employed during the rewarming period. 300 ml. of sodium bicarbonate-potassium chloride- calcium gluconate solution were infused during cooling and rewarming. The porta hepatis temperature fell to 34.1°C. over the following 56 minutes. The rectal temperature was then 32°C. and this rewarmed to 40°C. during the following 5 hours. Spontaneous pulmonary ventilation was particularly satisfactory while rewarming and consciousness was regained shortly after 5 hours post-perfusion. 150 ml. of blood drained from the chest and

were replaced by 525 ml. intravenously. The coagulation time was 8 minutes at 34.5°C. and reduced to 6 minutes at 40°C., with good clot retraction. The arterial pH measured at 37°C. did not fall below 7.25 during the whole procedure.

The dog made an uneventful recovery and was able to eat a light meal on the following day and to be exercised on the third day. He was observed for two months before being sacrificed and appeared normal in all respects during this period.

Observations

Blood coagulation time did not exceed 8 minutes in the post-experimental period.

EXPERIMENT 14 13.2.59.

A 16 kg. bitch was anaesthetised and prepared as in the previous experiment. During pre-cooling the porta hepatis temperature fell to 31°C. and on commencing the perfusion this temperature was reduced to 5°C. in 19 minutes. A period of 30 minutes total circulatory arrest and exsanguination was followed by rapid rewarming to 40°C. in 42 minutes, the temperature being held at this level for 20 minutes. An after-drop to 31.7°C., as measured in the rectal thermocouple, occurred during the following 1 hour 20 minutes and the animal then rewarmed to 39.5°C. 5 hours after perfusion, when consciousness was regained. At this time the arterial pH was 7.32 and had not fallen below 7.28 during the whole experiment. 350 ml. of the bicarbonate compound solution were used. A total of 475 ml. of blood drained from the chest and were replaced by 800 ml. intravenously. The animal made an uneventful recovery and appeared quite normal over an observation period of seven weeks.

Observations

Blood coagulation time did not exceed 6 minutes in the post-experimental period. A pre-experimental coagulation time was 4 minutes.

EXPERIMENT 15 16.2.59.

A 14.5 kg. dog was anaesthetised and prepared as in previous experiments. Pre-cooling to a porta hepatis temperature of 33.2°C. was followed by perfusion and rapid cooling to 4.6°C. in 22 minutes. A period of 30 minutes total circulatory arrest and exsanguination followed, after which the dog was rapidly rewarmed to 40°C. in 42 minutes, the temperature having been held at this point for 11 minutes. An after-drop to 31°C. measured by rectal temperature, occurred during the next 1 hour 18 minutes, following which the dog rewarmed to 40°C. in 5 hours 45 minutes after perfusion ceased. 350 ml. of bicarbonate compound solution were used and the arterial pH did not fall below 7.322. Blood coagulation was satisfactory throughout the post-operative period, being 4½ minutes at 32.2°C. and 4 minutes at 38°C. Chest drainage totalled 90 ml. and 550 ml. were given intravenously during the recovery period. The dog made an uneventful recovery and appeared perfectly normal during a seven weeks period of observation.

EXPERIMENT 16 20.2.59.

The experiment was repeated on a 12.5 kg. dog using the same technique as in the previous experiments of the series. Pre-cooling to a porta hepatis temperature of 32.8°C. was followed by perfusion and rapid cooling to 5°C., the latter occupying 17 minutes. A 30 minute period of total circulatory arrest and exsanguination was followed by rapid rewarming to 40°C. at which the temperature was held for 6 minutes. The rewarming was completed in 39 minutes. 300 ml. of the bicarbonate compound solution were used and the arterial pH did not fall below 7.26 during the experiment or the immediate post-operative period. An after-drop in porta hepatis temperature to 31.8°C. occurred, after which the rectal temperature steadily rose from 31.4°C. to 39.3°C. over the following 5 hours, when the dog regained consciousness. Spontaneous pulmonary ventilation improved progressively from 33°C. onwards and blood coagulation in the wounds appeared satisfactory. 170 ml. of blood drained from the chest and were replaced by 450 ml. intravenously.

The dog had a satisfactory immediate convalescence and was able to take light diet on the second day. He was exercised on the fourth day. During the following week there were signs of a pleural effusion developing. It was aspirated, but

subsequently became infected and the dog was destroyed on the 14th day. At post mortem there was an empyema of the right anterior chest with a localised pericarditis and small pericardial effusion. Apart from pallor, all other organs appeared normal.

EXPERIMENT 17 23.2.59

The experiment was repeated on a 14 kg. dog using the same technique as in the previous experiments. Cooling to 5°C. occupied 19 minutes and following 30 minutes total circulatory arrest and exsanguination, the dog was rewarmed to 40°C. and the temperature held at this point for 7 minutes. 350 ml. of sodium bicarbonate solution were used during this time and the arterial pH did not fall below 7.28. An after-drop in temperature to 32°C. of both porta hepatis and rectum, occurred over the following 1 hour 30 minutes; the rectal temperature then rose to 39.5°C. 6 hours after completing the perfusion. Consciousness was regained for a short period but approximately 45 minutes later the arterial pressure slowly decreased from 110 - 120 mm. Hg. Blood coagulation time was then 5 minutes. 130 ml. of blood had drained from the chest and were replaced by 250 ml. of blood. The pressure fall did not respond to further transfusion. A total of 650 ml. had been given when the dog collapsed and died.

At post mortem there were approximately 200 ml. of blood in the right thoracic cavity and 50 ml. in the pericardium. There was also partial collapse of both lungs, especially on the right side. A flap of pericardium had acted as a valve, allowing blood to be sucked into the pericardial sac from an uhdrained part of the thorax with resultant cardiac tamponade. Other organs appeared normal.

EXPERIMENT 18 27.2.59.

The experiment was repeated on a 14 kg. dog using the same technique as in previous experiments, with the exception that a period of 45 minutes total circulatory arrest with exsanguination was observed. Cooling to a porta hepatis temperature of 4.6°C. occupied 21 minutes which were followed by the 45 minutes total circulatory arrest and exsanguination. Rewarming to a porta hepatis temperature of 40°C. and maintaining that temperature for 15 minutes occupied a further 39 minutes. 400 ml. of the sodium bicarbonate compound solution were used and the arterial pH did not fall below 7.29 during the experiment. The pattern of recovery was similar to that of previous experiments. 50 ml. of blood drained from the chest and were replaced by 550 ml. intravenously, without evidence of over transfusion. The dog had an uneventful convalsecence and was observed for 6 weeks, during which time he appeared to be perfectly normal.

Observations

Extension of the period of total circulatory arrest from 30 minutes to 45 minutes did not raise any new problems, nor was any alteration in the degree of metabolic control required.

EXPERIMENTS 19 2.3.59.
20 9.3.59.
21 13.3.59.
22 23.3.59.

These experiments were conducted on dogs weighing 13.5 kg., 12.5 kg., 15 kg. and 17 kg. A precisely similar technique to that previously described was used, all being cooled to porta hepatis temperatures of 4.6°C. or below after which a period of total circulatory arrest of 45 minutes, combined with exsanguination, was observed. In dogs 21 and 22 a right ventriculotomy was performed during this period and the tricuspid valve inspected. There was only a small quantity of blood in the right ventricle which, after aspiration, left a bloodless field and a flaccid heart muscle. The ventricle was then filled with saline and the ventriculotomy closed with a continuous silk suture. Rewarming in the four experiments was accomplished in periods varying between 35 and 37 minutes, and all made a satisfactory immediate recovery. In dogs 21 and 22 there was no haemorrhage from the ventricular wounds and normal cardiac activity was restored at 14.6°C. and 13.9°C. respectively.

Dog 19 died suddenly $2\frac{1}{2}$ hours after perfusion, when the rectal temperature was 36.4°C. and when breathing spontaneously. At post mortem there was complete atelectasis of both lungs, and a large plug of viscid mucus lodged at the tracheal bifurcation.

Dogs 20, 21 and 22 made uneventful recoveries and were

observed for periods of two to five weeks before being sacrificed.

The relevant details of these experiments are summarised in Appendix Tables (i) to (vi).

Observations

In experimental dogs 19 and 22 a worm-like cardiac contraction, recurring every 30 seconds, was noted during the period of total circulatory arrest. This continued into the rewarming period to become established as an effective cardiac systole. This was presumably due to local rewarming of the heart. The ambient temperature in both cases was 21°C.

EXPERIMENT 23 29.5.59.

This experiment was performed to determine whether the somewhat cumbersome method of pre-cooling the experimental animal to 32°C. - 34°C. prior to perfusion, was necessary.

A 13.5 kg. bitch was anaesthetised with intravenous sodium thiopentone and pulmonary ventilation maintained as in previous experiments. When the surgical exposure was completed, 5 mg. heparin per kilogram body weight were administered intavenously and the catheters inserted. Porta hepatis, muscle and rectal temperatures were respectively 37°C., 36.8°C. and 37°C. After commencing perfusion these temperatures were rapdily reduced to 4.5°C., 22.6°C. and 11.5°C. within 29 minutes. The perfusion was discontinued, the animal exsanguinated and ice packs placed on the head. After a 45 minute period of total circulatory arrest the ice packs were removed, the perfusion restarted with rapid rewarming and the assistance of infra red heaters. At a porta hepatis temperature of 15°C. one of the arterial lines became disconnected, with considerable loss of blood and the mean arterial pressure fell to 0. The heart had not recommenced systole at this point. The tube was repaired and the perfusion resumed after approximately 5 minutes delay. 400 ml. of heparinised blood were added to the oxygenator to compensate for losses. After this episode the animal was rewarmed to 40°C., at

which point the temperature was held for 5 minutes, giving a total rewarming time of 36 minutes. Cardiac systole recommenced at 16.4°C. and satisfactory action was observed subsequently. 400 ml. of bicarbonate compound solution were required during the perfusion period and the arterial pH did not fall below 7.295.

Temperature changes and pH and mean pressure and perfusion rate are shown in Figure 34.

There was an after-drop of porta hepatis temperature to 32.7°C. when the pH also fell to 7.160; a further 150 ml. of bicarbonate compound were given to compensate this. A steady rise in the rectal temperature followed and reached 40°C. 4 hours after completing the perfusion. Spontaneous respiration occurred at 34.5°C. and there was no problem with blood coagulation or excessive bleeding from the wounds.

The bitch, however, did not regain consciousness and a period of 12 hours elapsed before she awakened, by which time the rectal temperature was 38.7°C. Thereafter she made a normal recovery and was exercised on the third post-experimental day. She was observed for a period of eight months and behaved normally in every respect.

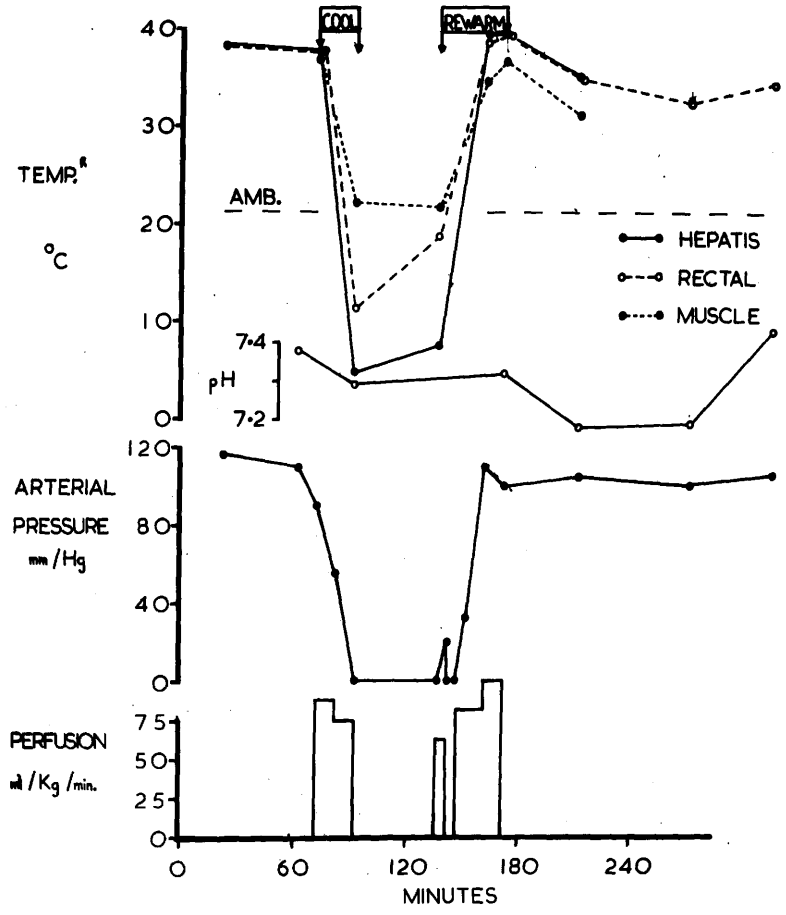
COOL
REWARM
TEMP.R
°C
40
30
20
10
0
AMB.
HEPATIS
RECTAL
MUSCLE
7·4
pH
7·2
ARTERIAL
PRESSURE
mm/Hg
120
80
40
0
PERFUSION
ml/Kg/min.
75
50
25
0
0
60
120
180
240
MINUTES

Figure 34.

Observations

1. Pre-cooling of muscle was not necessary for survival in this experiment.

2. Increasing the administration of bicarbonate compound solution by approximately 50 per cent was required to prevent the pH falling below 7.295 during the experiment.

3. The delayed recovery of consciousness could not be accounted for by anaesthetic or sedative drugs given. The 5 minute period of hypotension at 15°C. may have contributed to this delay.

CHAPTER VII

ANALYSIS AND CONCLUSIONS

A total of 56 experiments, divided into four series, have been presented. In each series a basic problem existed as follows:

1. Series III: Experiments 1 - 7.

The induction of deep hypothermia below 10°C. with an extra-corporeal pump oxygenator and heat exchanger and the effect on the heart both in cooling and rewarming.

2. Series IV: Experiments 1 - 20.

Whether such induction of deep hypothermia was compatible with survival.

3. Series V: Experiments 1 - 6.

The induction of deep hypothermia to 10°C. or below, combined with a period of total circulatory arrest at low temperature and its effect on the heart.

4. Series VI: Experiments 1 - 23.

Whether such total circulatory arrest combined with exsanguination for periods of 30 to 45 minutes, was compatible with survival.

Series IV and VI were subdivided, the technique in the initial experiments varying to answer immediate problems. A basically standard technique was used in the final experiments to confirm the results.

The results of the four series of experiments are tabulated below.

Series	Exp.	No. of Exps.	Results	Average
III	1- 7	7	Cardiac recovery in 7	100%
IV	1-12	12	Survival in 2	16.7%
	13-20	8	Survival in 6	75%
V	1- 6	6	Cardiac recovery in 2	33 1/3%
VI	1-12	12	Survival 0	0%
	13-23	11	Survival 9	81.8%

Since many of the problems involved in the study of deep hypothermia, with or without total circulatory arrest and exsanguination are common, it is proposed to consider these as a whole under the relevant headings.

TEMPERATURE

The temperature recorded in the porta hepatis was used as an overall index of the degree of cooling and rewarming during the experimental period. The blood entered the aorta at 0°C. as shown in Figure 35.

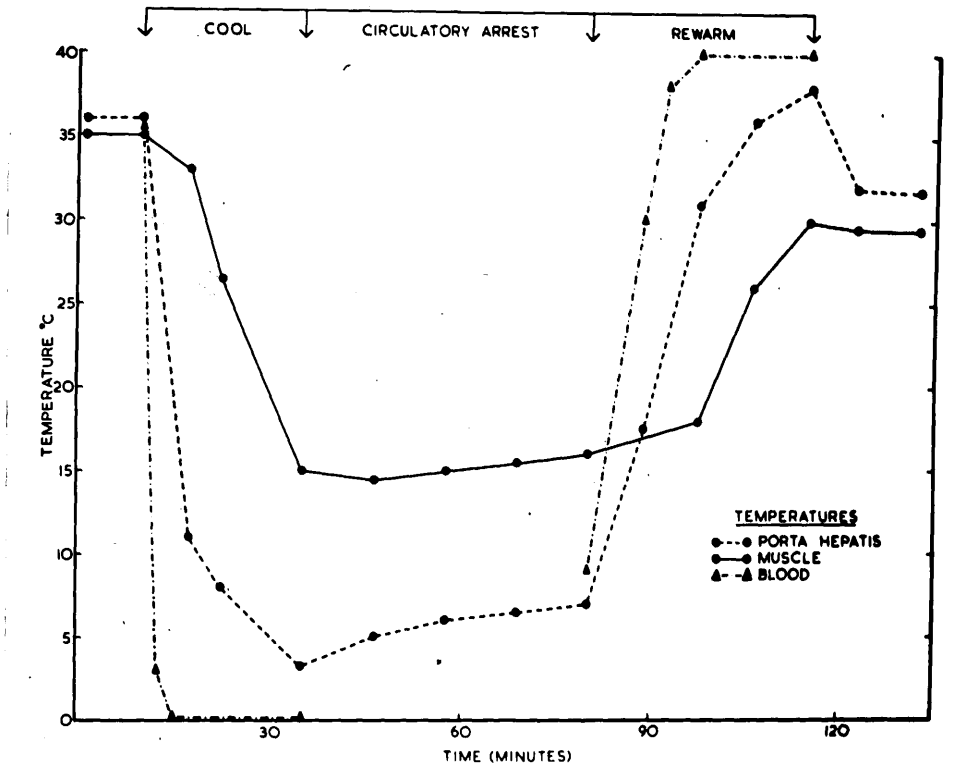

Figure 35.

A temperature gradient existed between the aorta and the surface tissues. This was maximal at the skin which was at or near the ambient temperature during the period of circulatory arrest (Figure 18). The oesophagus was considered an unreliable index of body temperature for the following reasons:

1. Because of its close proximity to the heart and the

aorta into which blood is perfused at a temperature of 0°C., the reading would be too low during the induction of hypothermia.

2. Because of the presence of an open thoracotomy wound and the consequent nearness of ambient temperature, the reading would be too high during the later stages of total circulatory arrest.

The rectal temperature is also unreliable in the presence of altered blood haemodynamics (Cooper and Kenyon, 1957). The porta hepatis which is anatomically closely related to many of the major organs of the body with the exception of the brain, the heart and the lungs, was therefore chosen as the index of the degree of hypothermia.

In the initial experiment (III/1) a porta hepatis temperature of 17°C. was produced but in the following 55, this temperature was reduced to 12°C. or less, the majority below 5°C. The range was between 12°C. and 3.4°C.; a mean of 5.1°C.

RATE OF TEMPERATURE CHANGE

The rates of reduction of temperature on cooling and of increase on rewarming were proportional to the extra-corporeal perfusion rate and also varied with the type of heat exchanger used (Table 1). The Mark II heat exchanger proved the most efficient and most satisfactory in practice.

With the slow cooling and rewarming rates and low flows

used in the experiments of Series III and the majority of experiments of Series V, a more effective total body cooling was produced (Figures 15, 17 and 27). Rapid cooling and rewarming resulted in wider temperature differences between porta hepatis and muscle (Figures 18, 26, 29 and 34). The results for both are also shown in Table 1.

There is a theoretical objection to wide temperature gradients between blood and tissues in that the O_2-dissociation curve shifts to the left (Brown and Hill, 1923. Figure 36).

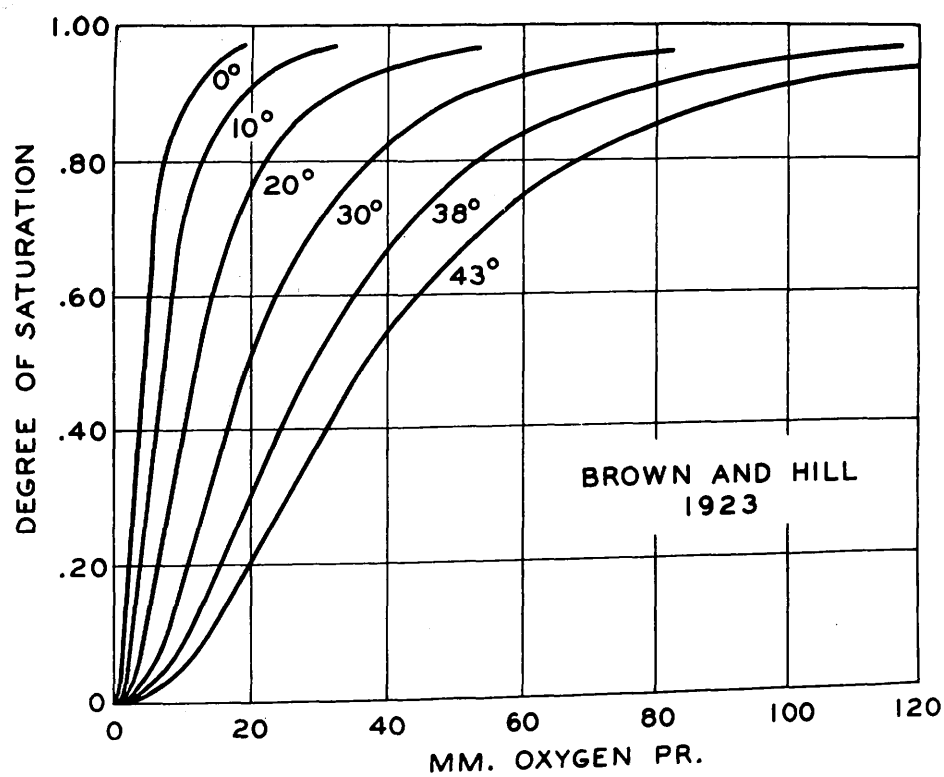

Figure 36.

This factor also applies to the CO_2-dissociation curve with the possible result that sudden rise of temperature may cause a spontaneous effervescence with the production of gaseous micro-emboli. Emperiments VI/7, 8 and 9 were performed with this in mind and a temperature gradient not exceeding 10°C. was observed, but did not result in survival. There was no suggestion of gas embolism in any of the survivors of Series IV and VI with the rapid cooling and rewarming methods employed. Moreover, these methods which could easily be produced by wide temperature gradients, offered the particular advantage of satisfactory blood coagulation during the post-operative period. It is, however, noteworthy that increased foaming of the blood in the oxygenator was frequently observed at low temperatures.

TEMPERATURE GRADIENTS IN THE BODY

Cooling

When hypothermia was induced, the temperature of the blood entering the aorta, rapidly fell to 0°C. and was followed by a fall in the temperature of the porta hepatis, the rectum and muscle, in that order. The temperature of the heart and lungs were closely related to each other and 1° - 3° lower than that of the porta hepatis (Figure 27). Both rectal and muscle temperatures were higher, the brain temperatures, when measured (VI/4 and 5), reached a level of 10°C. or less.

Circulatory Arrest

In experiments with total circulatory arrest, the low temperatures of the porta hepatis, rectum and brain showed a rise of a few degrees. The muscle temperature generally showed a slight fall, followed by a rise (Figure 35) but on a few occasions (V/1, 2 and 5; VI/23) there was a steady fall. It is noteworthy that in the latter experiment, when the dog was exsanguinated, the muscle temperature was above ambient, whereas in the former instances, the dogs were not exsanguinated and the muscle temperatures were below ambient.

These results suggest that during periods of circulatory arrest there is little or no heat production by the tissues and that the deep core temperature tends to equilibrate with that of the surface which is at or near ambient temperature. The fall in muscle temperature, in the experiments without exsanguination, could be attributed to a gravitational flow of cold blood from the core to the muscle. This might also account for the minor initial fall of muscle temperature as shown in Figure 35.

Rewarming

The reverse of events occurred during rewarming and the results of Series IV emphasized the need for adequate rewarming, both by blood stream and by provision of extra-corporeal heat.

Series	Exps.	Post-Expt. T^H °C. Mean	% Survivors
IV	1-12	34.3	16.7
	13-20	40.0	75

When rewarming was complete and perfusion discontinued, the porta hepatis temperature fell. This after-drop varied between 2.5°C. and 10.8°C. (mean 7.2°C.). A similar after-drop in rectal, brain and occasionally muscle temperature occurred. Brain and usually the rectal temperatures fell until they equilibrated with the rising muscle temperature. This period varied between 25 minutes and 4.25 hours. In the experimental animals that survived, the initial rise was slow but thereafter they rewarmed more rapidly; the time to reach 38.5°C. varied between 14 hours and 2.75 hours (mean 6.15 hours); this represents a rise of temperature of 0.36° 3.64°C. per hour.

A post experimental elevation of temperature to 40° - 41°C. was usual in uncomplicated survivals and it returned to normal within 24 to 36 hours.

THE HEART

Ventricular Fibrillation.

Ventricular fibrillation was not a serious problem with the technique described. This event was observed in 19.6 per cent of the 56 experiments occurring either on cooling or rewarming, or on both. Spontaneous conversion occurred in 5 experiments;

potassium citrate or cold conversion defibrillation (Kenyon and Ludbrook, 1957) was produced in 3 experiments and in 3 experiments irreversible ventricular fibrillation was observed. The latter was observed in the acute experiments (V/1, 4 and 5) with periods of 30 or more minutes total circulatory arrest. Local cooling of the heart, as in experiments V/5 and 6, did not prevent the onset of fibrillation. Neither the extent to which the animals were cooled nor the duration of the total circulatory arrest, when produced, appeared to influence the incidence of ventricular fibrillation.

When the incidence is compared with the different methods of arterial cannulation, the following results are obtained.

No. of Exps.	Arterial Cannulation	Ventricular Fibrillation		
		Irreversible	Reversible	Nil
39	Subclavian	3	8	28
17	Iliac	0	0	17

Thus it appeared that when ventricular fibrillation occurred it was due to rotation of the subclavian cannula which, while in the aortic arch, ejected the jet of blood in a downward direction. Reduction of pressure in the ascending portion of the aorta resulted in decreased coronary flow. This was insufficient to cause permanent cardiac damage in those experiments where rewarming was commenced immediately, but irreversible damage occured late

during total circulatory arrest, when the heart had rewarmed to ambient or near ambient temperature. The metabolic acidosis produced during the period of total circulatory arrest would undoubtedly depress cardiac function but the degree of acidosis produced would not, by itself, appear to induce fibrillation at this stage of the experiment.

Cooling

When cooling commenced the cardiac action slowed progressively and the rate was directly proportional to the temperature recorded in the porta hepatis, as far as 18° - 22°C.

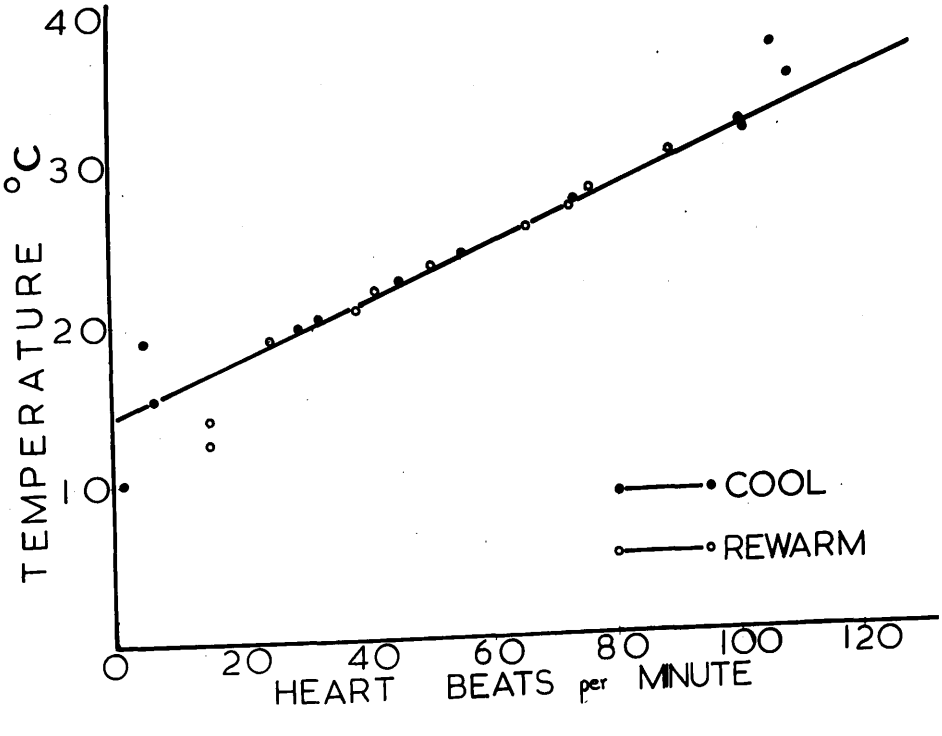

Figure 37

This also applied to those hearts in which fibrillation occurred, up to the time when the latter was observed. Cardiac arrest occurred at temperatures varying between 8.5°C. and 19.8°C. (mean 13°C.) in all experiments without ventricular fibrillation. The E.C.G. changes during perfusion hypothermia have been previously reported in some detail by Kenyon and Ludbrook (1957) and the findings were confirmed on many occasions in subsequent experiments. Briefly, there was a progressive decrease in cardiac conduction manifest by broadening of the P waves and QRS complexes. The PR and QT intervals became progressively longer (Figure 38).

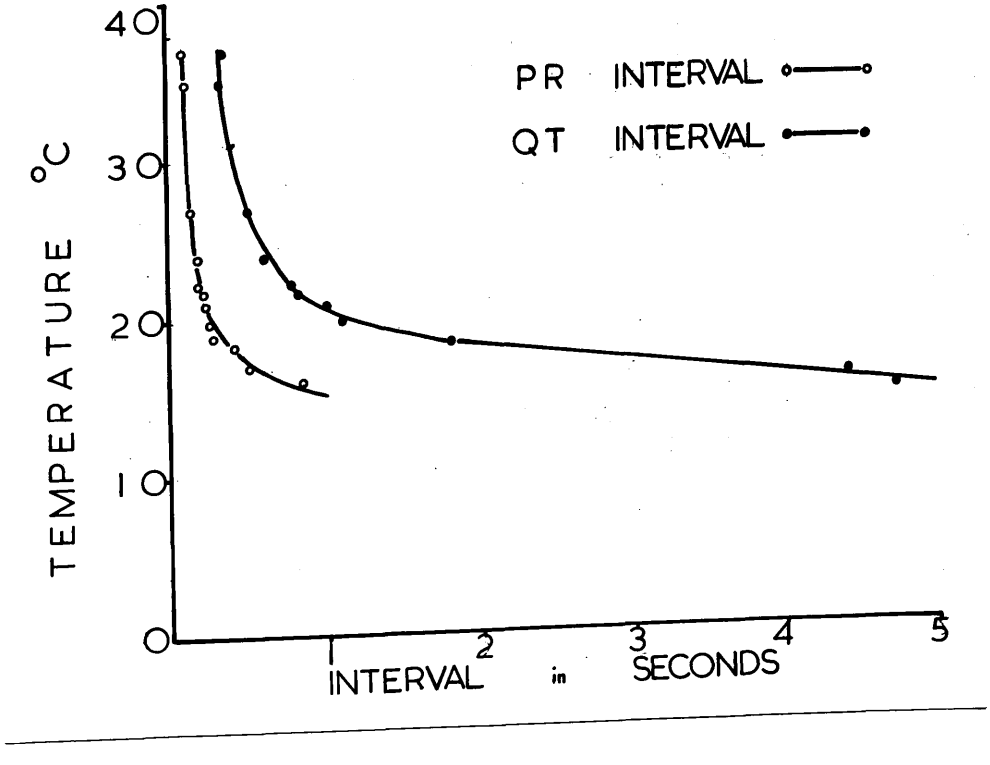

Figure 38.

Below 15-20°C. any one of the following events could occur:

(i) Complete absence of electrical activity.

(ii) Persistent P waves with no QRS complexes.

(iii) Regular ventricular complexes with retrograde ecitation of the auricle.

(iv) Regular ventricular complexes only. Occasionally these were followed by a sinusoidal recovery complex.

(v) Ventricular fibrillation.

It was then stated that "which of these events occurred in any one animal appeared to depend to some extent on the output of the cardiac bypass". There is no reason to alter this opinion, but it must be added that the directional flow from the arterial cannula is also of importance, as described previously.

CARDIAC ARREST AND TOTAL CIRCULATORY ARREST.

During these periods the heart remained soft and flaccid, and no contraction was observed with the exception of experiments VI/19 and 22. A slow worm-like contraction was noted, recurring every 30 seconds, during the latter period of the total circulatory arrest. At this time a raised epicardial temperature was noted which was near the ambient temperature of 21°C. but the transmural temperature gradient was not sought. This contraction most probably resulted from rewarming of the cardiac muscle as a whole. These slow contractions would not have embarrassed a major surgical

procedure on the heart.

The period of cardiac asystole varied between 14 minutes and 108 minutes (mean 36.8) in experiments of Series III and IV, without perfusion arrest, and 47 minutes and 108 minutes (mean 77.4) in V and VI, with periods of 20 to 60 minutes of total circulatory arrest (Table iii).

REWARMING

On rewarming, the E.C.G. showed the first sign of activity, with reappearance of P waves at or near 10°C. As the temperature rose 1° - 3°, ventricular complexes appeared, with the normal sequence of conduction. The rate increased and conduction time decreased with rising temperature (Figures 37 and 38). The first cardiac contractions appeared after the electrical activity commenced. In 45 experiments without fibrillation, they appeared between 11°C. and 26.5°C. (mean 15.1). In all these experiments the immediate recovery of cardiac function was satisfactory. With adequate rewarming, as in experiments Series IV/13-18, and with additional metabolic control, as in Series VI/12-23, the complete and ultimate recovery of the heart raised no problem.

THE AETIOLOGY OF VENTRICULAR FIBRILLATION

A considerable amount of research has failed to reveal the cause of ventricular fibrillation. Most of this, as indicated in Chapter I, referred to the purely physiological and biochemical

effects of hypothermia on the heart, and relatively little attention has been paid to the biophysical effects of cold on cardiac muscle. Szent-Gyorgyi (1953) has shown that in the frog, skeletal and cardiac muscular contraction depends upon the shortening and elongation of protein complexes. The enzyme Actin combines with muscle protein Myosin to form Actinomysin.

$$\text{Actin} + \text{Myosin} \rightleftharpoons \text{Actinomysin}.$$

This reaction is rapidly reversible. The molecules of Myosin are arranged in long chains and in Actinomysin these chains assume a zig-zag pattern with physical shortening of the molecules and also the muscle fibre which is composed of groups of these molecules. If this reaction of the poiklotherm applies to the homeotherm, the effects of cold on the enzymes will prolong both reaction and recovery period, and on the proteins will increase the viscosity and reduce the efficiency of the biophysical reaction. In the small mammal such as the rat and hamster, cooled by surface methods (Andjus, 1951; Andjus and Smith, 1955), the core temperature may be rapidly reduced, with cold arrest of the heart before irreversible damage occurs. In larger mammals and man cooled by surface methods, the core temperature is more slowly reduced, and ventricular fibrillation with irreversible anoxic damage to cardiac muscle is produced before cold arrest can occur. Thus some form of extra-corporeal mechanical

assistance must be given to the heart during cooling and rewarming to avoid this event (Kenyon and Ludbrook, 1957).

VASCULAR RESPONSES

These have not been studied in detail but a few general observations are worth noting. When the venae cavae were catheterised, a fall of mean arterial pressure of 10 - 15 mm. Hg. was the rule and was caused by mechanical obstruction to the venous return. When the extra-corporeal bypass was commenced, the mean arterial pressure varied proportionately with the perfusion rate. At this stage there appeared to be a partial loss of vascular tone, since minor variations in the pump output were reflected by corresponding rise or fall in the mean arterial pressure.

On cooling there was a precipitate fall of arterial pressure until the point of cardiac arrest, when the former levelled off in the region of 40 - 50 mm. Hg. During the cooling stage it was usual to add approximately 200 ml. of the priming agent to the oxygenator to maintain an adequate venous return and rate of cooling. In those experiments in which circulatory arrest only, was produced, the arterial pressure was constant at 5 - 12 mm. Hg. but with exsanguination this fell to 0 mm. Hg.

On rewarming the pressure and perfusion events occurred in the reverse order to those on cooling and the maximum perfusion

rate was reached before discontinuing the extra-corporeal circulation. In the dogs which survived, a large positive balance of blood was required, the greater part of which was given during the early post-experimental period. These results are tabulated below.

Expts.	COOLING		REWARMING		RECOVERY
	Mean Perfusion Rate ml/kg/min	Infused ml.	Mean Perfusion Rate	Infused ml.	+ve balance ml.
III 1- 7	40.4	150	42.8	162.5	
IV 1-12	54.8	204.1	57.1	125	
13-20	59.1	168.8	68.3	100	+70
V 1- 6	52.4	250	58.6	100	
VI 1-12	52.3	220.8	60	170.8	
13-23	63.9	263.6	73.3	184.1	+387.7

All these observations suggest a complete loss of vascular tone as the animals were cooled to the low core temperatures and superimposed on this, an increasing viscosity of the blood as the low temperatures were reached, resulting in a fall in venous return and a decreased perfusion rate. During rewarming, a recovery of vascular tone occurred at approximately the same time as cardiac systole commenced, to be followed by an active vasodilation, which continued throughout the rearming period. These events are particularly well shown in Experiment III/5 (Figure 17). In those experiments with total circulatory arrest, an even larger

positive balance of blood was required in the post-experimental period, to maintain an adequate arterial pressure. This suggested a continued vasodilatation, probably in the relatively uncooled muscle vessels. Noradrenaline infusion was used only in emergency in some of the survival experiments without circulatory arrest, but the use of this drug was discontinued in subsequent experiments. In all the unsuccessful experiments of both survival series, there was never any suggestion of over-transfusion, as evidenced by pulmonary congestion or splenic enlargement.

THE BLOOD

Haemolysis. In those experiments in which plasma haemoglobin was measured the post-perfusion increases varied between 112 and 15 mg./100 ml. High values were noted when dextran priming of the apparatus was used in the early acute experiments, and low values were the rule in the later survival experiments.

Plasma Fibrinogen was measured on three occasions. A marked reduction occurred in experiment IV/9 but in IV/10 and V/5 satisfactory levels were maintained.

White blood cells and platelets. Almost complete or total absence was noted in experiments IV/9 and V/5, but in IV/10, 11 and 12 normal levels were maintained. Normal levels were also observed in later experiments in Series VI.

Plasma Serotonin (5-hydroxytryptamine). No increase was noted in experiments VI/2 and 3.

Coagulation of the Blood. A prolonged coagulation time was noted at temperatures between 28°C. and 33°C. in experiments IV/1-12, when inadequate rewarming resulted in a marked after-drop in the body temperature. Prolonged perfusion times also delayed blood coagulation as evidenced in experiments VL/1-12. This latter fact could not be correlated with any absence of the coagulation factors measured.

The reason why 10 mg. heparin per kilogram body weight preserved the clotting factor in experiments IV/9-20, V/6 and VI/1-6 and subsequently, 5 mg. per kilogram gave satisfactory results, is not clear. It is, however, possible that an excessive amount of Antifoan A was used in the preparation of the oxygenator, but on rechecking the methods, no evidence was available to confirm this possibility.

THE BRAIN

The electro encephalogram was observed in six experiments and in two of these the extra-dural temperature was also observed in addition to that of the porta hepatis. These results are tabulated below.

Expt. No.	COOL E.E.G. absent Hepatis T°C.	Brain T°C.	REWARM E.E.G. present Hepatis T°C.	Brain T°C.
VI/4	18.2	21	21	21.2
5	19	19.8	24.8	20.6
6	19.6		25	
7	20.5		23	
8	18		22.5	
9	19.4		22.4	
Mean:	19.1	20.4	23.1	20.9

Thus E.E.G. activity disappeared at 20.4°C. and reappeared at 20.9°C., the corresponding porta hepatis temperature range being 19.1°C. to 20.5°C. and 21°C. to 25°C. respectively. Woodhall, Reynolds, Mahaley and Sanders (1958) have reported similar results in selective cooling of the brain by local perfusion.

There was no evidence of depressed cortical function in any of the surviving dogs and they behaved normally during the period of observation.

METABOLISM

In experiment III/1, in which the dog was cooled to 17°C. and rewarmed immediately, a pH of 7.12 was noted, but recovered to near the pre-perfusion level of 7.16. In experiments III/2 and 3, when the dogs were cooled to below 8°C. a progressive fall of pH was noted (Figures 11 and 14). However, with the survivors of Series IV/2 and 3, and the 75 per cent survival in the latter

part of the series, these findings were attributed to a combination of respiratory and metabolic acidosis produced by the relatively inefficient respiratory apparatus in the former, and the experimental procedure in the latter.

The observation of a pH of 6.9 during experiment VI/8 immediately gave the reason for the failure to survive in earlier experiments in Series VI. Figure 32 for experiment VI/9 reflects a severe degree of metabolic acidosis and a lesser degree of respiratory acidosis, which was only partially corrected by 100 ml. of isotonic sodium bicarbonate administered intravenously. The metabolic acidosis was subsequently controlled by adequate infusion of sodium bicarbonate monitored by the arterial pH. A comparative chart of uncontrolled (Experiment VI/9) and controlled metabolism is shown in Figure 39. The temperature illustrated is a mean of the two porta hepatis temperatures.

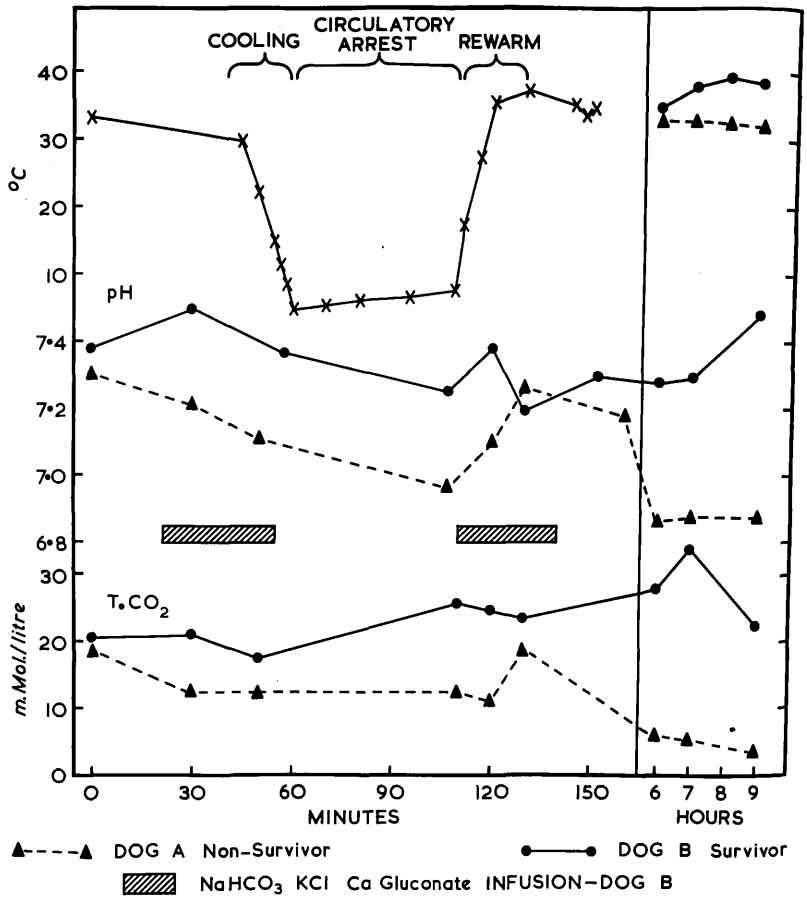

Figure 39

The quantity of sodium bicarbonate required to maintain a pH of 7.2 or more during the experimental period varied between

5.33 mEq/Kg. and 5.38 mEq/Kg. A further administration was often required during the post-operative period. In experiment VI/23 when the dog was not pre-cooled, the infusion was increased to 7.36 mEq/Kg. The significance of pH values measured at normal body temperatures, when the experimental animal is at the low temperatures observed, is detatable due to altered pK_1 changes, increased solubility of CO_2 and altered buffering capacity of haemoglobin and plasma proteins. An added factor is the temperature gradient in the animal, where the core temperature may be in the region of 5°C. and that of the muscles at 20°C. Severinhaus and Stupfel (1956) have produced a nomogram for correcting pH values down to 10°C., but even with this in mind the pH, measured at 37.5°C. proved to be of value in the metabolic control when correlated with the physiological responses of the animal. This correction of the acidosis was only partial, the final balance being left to the dog's own homeostatic mechanisms.

The metabolic rate of tissues is proportional to the oxygen consumption or Q10, which varies directly with temperature. For metabolic and rhythmical processes the Q10 is 3, for rates of contraction a value of 2, and for physical processes, 1. (Brown, 1956). Thus for a fall of 10°C. in temperature, the oxygen consumption of the liver would fall to 33.3% of normal. Fuhrman (1956) has

related the oxygen consumption of rat tissues to temperature as shown in Figure 40.

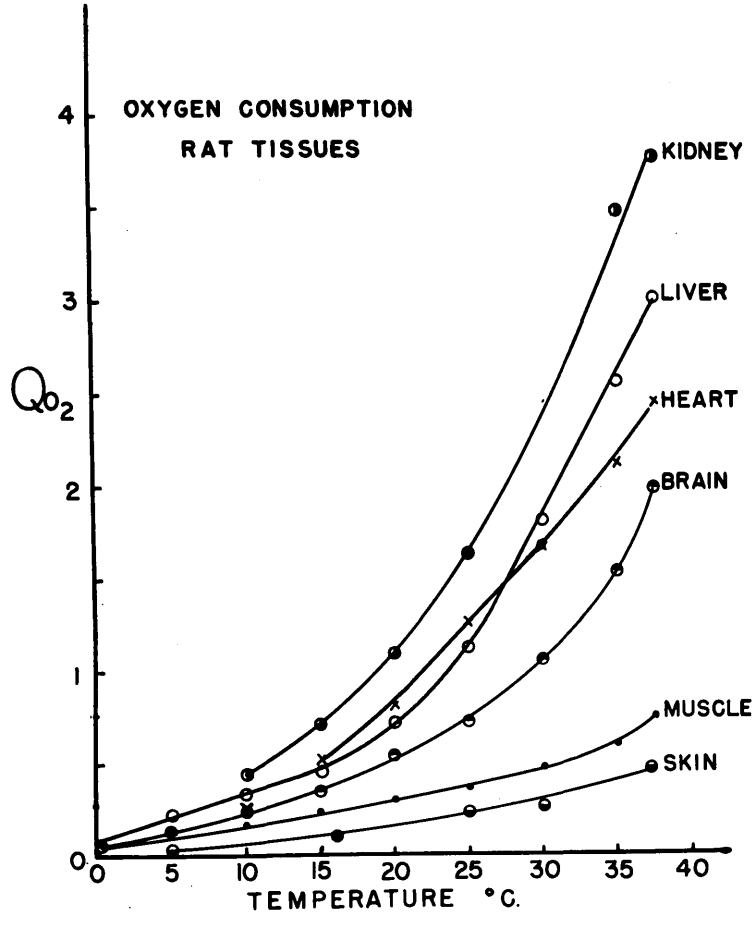

Figure 40.

In those experiments in which total circulatory arrest was produced the mean temperature of the tissue during the period of

arrest would give a close approximation of the metabolic rate. For Series V and VI the following results were obtained.

Temperatures of porta hepatis, rectum, muscle and brain in acute and survival experiments during total circulatory arrest.

Series	Hepatis °C.	Rectum °C.	Muscle °C.	Brain °C.
V/1,2,4,5,6,	6.1	13.3	15.1	
VI/ 1-12	6.0	12.4	15.6	8.3
13-23	6.8	13.2	18.6	
Mean:	6.3	13.0	16.4	8.3

When these mean values are related to Fuhrman's oxygen consumption data for the rat and assuming that the temperature of the porta hepatis closely approximates to that of the liver and kidney, the following reduction in metabolic rate will apply:

Liver 8 % of normal.
Kidney 8.5% " (approx.)
Brain 10 % "
Muscle 30.5% "

Thus under the experimental conditions described, there is an appreciable reduction of oxygen consumption of many of the essential organs but a relatively small reduction in that of muscle. The muscle mass may well have accounted for the greater part of the desaturated blood noted on recommencing the perfusion after the period of circulatory arrest and also the metabolic acidosis, as expressed by the fall in pH and pCO_2. An additional factor implicating the muscle in the production of acidosis was

the increased infusion of sodium bicarbonate required in experiment VI/23 when pre-cooling of the muscle was not instituted. As stated above, the Q10 of diffusion is 1, whereas the Q10 of metabolic processes is 3, and the rate of diffusion of metabolites from the cell to the blood stream would be expected to exceed the rate of production. However, without circulation it is possible that diffusion across the cell membrane was reduced to zero and the exsanguination may well have expedited this process.

Recommencing the circulation and rewarming would be expected to correct this process and appeared to do so in part, but a second and more marked fall of pH was observed on discontinuing the perfusion (Figure 40) and accompanied the after-drop in temperature. The after-drop did not usually exceed 8°C. and would be insufficient to reduce muscle metabolism to any extent. These observations suggest that there was either a further production of acid metabolites from the body cells in general, or alternatively a temporary damage to the muscle cell membrane during the period of circulatory arrest, resulting in a depression of the diffusion rate, which only recovered during the rewarming and post-rewarming stages, with progressive release of acid metabolites. It is very probable that both factors were responsible in the experiments described.

Serum Potassium. In six experiments in Series IV there was a

mean fall of 0.3 mEq/litre during the perfusion period, while in Series VI the mean fall was 1.7 mEq/litre. In three experiments in Series VI a venous blood sample was taken immediately after recommencing perfusion. This showed a rise of serum potassium of 1.3 - 5.5 mEq/litre. This latter observation is an added factor in the possible changes in the cell membrane discussed above.

Serum Sodium and Serum Osmolarity showed no significant changes which could not be accounted for by additions of sodium chloride or bicarbonate to either perfusion or infusion.

RENAL FUNCTION

Detailed studies of renal function were not made in the experiments described. There was a complete suppression of urinary output during cooling, circulatory arrest and the early rewarming period. Occasional estimation of the post-experimental urine volume and electrolyte content suggested satisfactory glomerular and tubular function and the surviving dogs showed no clinical evidence of depressed renal function.

CONCLUSION

The technique developed in the series of experiments described, has permitted the lowering of deep body temperature to the region of 5°C., at which level complete circulatory arrest, combined with exsanguination, was possible for periods up to 45 minutes. In the final group of eleven experiments, nine dogs survived and were perfectly normal in all respects.

With the methods used ventricular fibrillation raised no problem and did not occur in the final series of experiments.

A metabolic acidosis, most probably generated in the relatively uncooled muscles, occurred after periods of circulatory arrest and required careful control during cooling, rewarming and the post-experimental periods.

Failure of the blood to coagulate did not occur in the post-experimental period, provided the deep body temperature had reached at least 33°C. on rewarming and the extra-corporeal perfusion time had not materially exceeded 60 minutes. This latter factor demanded the use of efficient heat exchangers to produce rapid cooling and rewarming.

There is no reason why the period of circulatory arrest should not be prolonged but further research and experience will be necessary to confirm this supposition.

APPENDIX

Tabulated Summary of Experimental Data.

(i) Cooling, Rewarming, Flow Rates and Post-operative Fluid Balance.

(ii) Temperatures after Reoovery.

(iii) Cardiac Asystole.

(iv) Temperatures on Completing Cooling and Rewarming.

(v) Temperatures at Beginning and End of Total Circulatory Arrest.

(vi) $NaHCO_3$ Infusion during Perfusion.

Abbreviations

T^H	-	porta hepatis temperature
T^R	-	rectal temperature
T^M	-	muscle temperature
T^B	-	brain temperature
T^C	-	cardiac temperature
VF	-	ventricular fibrillation
C	-	cold
K	-	potassium
Conv.	-	conversion

TABLE I.

COOLING- REWARMING- FLOW RATES and POST-OPERATIVE FLUID BALANCE.

				COOL			REWARM		
Series.	Exp. No.	Heat Exchanger.	Lowest T_{Ho_C}	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Recovery +ve Balance. mls.
III	1	Coil	17	105	17	100	148	20	150	-
	2	Coil	7.8	96	23	-	92	27	-	-
	3	Coil	6.0	66	41	100	71	43	100	-
	4	Coil	6.7	153	50	200	123	50	200	-
	5	Mark I	4.9	94	55	200	96	75	-	-
	6	Mark I	6.0	51	50	200	76	45	200	-
	7	Mark I	5.8	63	47.5	100	93	40	-	-
MEANS			7.7	89.7	40.4	150	99.9	42.8	162.5	-
IV	1	Mark I	8.0	36	60	400	37	60	-	+ 50
	2	Mark I	4.5	35	65	200	45	55	-	+100
	3	Mark I	12.0	40	70	150	40	70	-	-100
	4	Mark I	4.8	35	50	200	45	55	-	-250
	5	Mark I	6.3	38	40	200	49	55	-	+ 75
	6	Mark I	8.0	30	60	150	65	57.5	-	+100
	7	Mark I	9.5	32	55	200	47	60	-	- 50
	8	Mark I	4.7	55	47.5	200	50	50	-	+ 75
	9	Mark I	10.5	35	57.5	200	45	60	200	- 50
	10	Mark II	5.0	32	55	200	40	50	-	- 50
	11	Mark II	7.2	38	50	150	37	57.5	50	+ 50
	12	Mark II	6.4	30	47.5	200	43	55	-	+ 50
MEANS			7.2	36.3	54.8	204.1	45.3	57.1	125	0

TABLE I. continued.

COOLING- REWARMING- FLOW RATES and POST-OPERATIVE FLUID BALANCE.

				COOL			REWARM		
Series.	Exp. No.	Heat Exchanger.	Lowest T_{Ho_C}	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Recovery +ve Balance. mls.
IV cont.	13	Mark II	4.5	22	75.5	200	35	80	100	0
	14	Mark II	3.6	35	64.0	100	45	73	-	+100
	15	Mark II	5.0	22	56	200	35	64	-	+125
	16	Mark II	5.0	19	55	200	34	52	100	+100
	17	Mark II	4.8	22	62	200	42	75	100	+ 50
	18	Mark II	4.0	18	58	100	22	64	-	+175
	19	Mark II	4.0	16	52	150	32	65	100	-130
	20	Mark II	4.6	21	50	200	53	73	100	0
MEANS			4.4	21.9	59.1	168.8	37.3	68.3	100	+ 70
V	1	Coil	3.7	140	-	-	-	-	-	-
	2	Coil	4.8	72	57.5	100	80	60	100	-
	3	Coil	5.4	85	-	-	-	-	-	-
	4	Mark I	6.0	42	40	100	70	42.5	-	-
	5	Mark I	5.0	90	62	100	56	80	-	-
	6	Mark II	3.7	45	50	200	56	52	-	-
MEANS			4.8	79	52.4	250	65.5	58.6	100	-
	1	Mark II	3.6	26	53	200	55	68	-	+ 75
	2	Mark II	4.8	28	50	200	72	55	50	+100
	3	Mark II	4.2	33	55	250	60	63	-	+150
	4	Mark II	3.4	29	58	200	47	65	-	+180
	5	Mark II	4.2	56	53	200	107	58	-	+ 90
	6	Mark II	6.4	48	45	150	82	58	100	+160
	7	Mark II	4.3	51	40	150	49	52	-	+150
	8	Mark II	3.6	42	38	300	71	45	-	+100

TABLE I. continued.

COOLING- REWARMING- FLOW RATES and POST-OPERATIVE FLUID BALANCE.

				COOL			REWARM			
Series.	Exp. No.	Heat Exchanger.	Lowest T^{Ho}_{C}	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Time. min	Mean Perfusion Rate. ml/Kg/min	Infused mls.	Recovery +ve Balance. mls.
VI cont.	9	Mark II	4.8	12	63	100	64	67	100	+300
	10	Mark II	3.6	41	55	300	70	64	250	+ 50
	11	Mark II	4.8	52	58	300	33	60	250	+175
	12	Mark II	6.0	25	60	300	29	65	275	+175
MEANS			4.5	36.9	52.3	220.8	61.6	60	170.8	+142.1
	13	Mark II	4.8	18	50	250	25	68	150	+375
	14	Mark II	5.0	19	62	250	42	84	200	+325
	15	Mark II	4.6	22	53	250	42	60	200	+460
	16	Mark II	5.0	17	66	250	39	68	150	+280
	17	Mark II	5.0	19	68	250	37	75	200	+400
	18	Mark II	4.6	21	65	300	39	76	200	+500
	19	Mark II	3.2	25	68	300	42	75	150	+250
	20	Mark II	4.6	20	68	250	35	70	200	+400
	21	Mark II	4.0	16	60	250	37	75	175	+400
	22	Mark II	3.8	21	65	250	36	73	200	+375
	23	Mark II	4.5	29	78	300	36	82	200	+500
MEANS			4.5	20.6	63.9	263.6	37.3	73.3	184.1	+387.7

TABLE 2.

TEMPERATURES AFTER RECOVERY.

Series.	Exp. No.	T^H °C	After-drop °C	Duration min.	Time to Reach Normal (38-40°C) hours.
III	1	31.7	-	-	-
	2	31.8	-	-	-
	3	33.0	-	-	-
	4	32.4	-	-	-
	5	35.2	-	-	-
	6	33.0	-	-	-
	7	33.0	-	-	-
MEANS		32.9	-	-	-
IV	1	33.0	5.2	25	5½
	2	33.3	5.4	52	7
	3	33.2	4.5	45	6
	4	34.4	5.1	50	-
	5	34.3	5.7	51	-
	6	34.0	3.5	75	-
	7	34.0	6.0	58	-
	8	35.4	7.7	80	-
	9	32.7	4.2	255	9½
	10	34.6	5.5	120	-
	11	36.0	2.5	80	-
	12	36.7	7.2	120	7
MEANS		34.3	5.2	84.3	7
	13	40.0	5.0	55	14
	14	40.0	7.5	120	9
	15	40.0	8.5	240	9
	16	40.0	7.9	130	-
	17	40.0	9.5	76	5½
	18	40.0	9.0	87	4½
	19	40.0	8.7	78	-
	20	40.0	8.0	68	5
MEANS		40.0	8.0	106.7	7.8

TABLE 2. continued.

TEMPERATURES AFTER RECOVERY.

Series.	Exp. No.	T^H °C	After-drop °C	Duration min.	Time to Reach Normal (38-40°C) hours.
V	1	-	-	-	-
	2	32.3	-	-	-
	3	-	-	-	-
	4	31.0	-	-	-
	5	30.0	-	-	-
	6	35.0	-	-	-
MEANS		32.1	-	-	-
VI	1	40	7.6	63	6
	2	40	7.2	58	-
	3	40	6.5	44	5
	4	40	6.4	40	$5\frac{3}{4}$
	5	40	8.0	35	-
	6	40	10.8	50	-
	7	40	6.3	52	-
	8	40	5.0	60	-
	9	40	10.0	87	-
	10	40	7.5	53	$5\frac{3}{4}$
	11	40	6.1	45	6
	12	40	7.9	60	5
MEANS		40	7.4	53.9	5.6
	13	40	5.9	56	$3\frac{3}{4}$
	14	40	8.3	80	5
	15	40	9.0	78	$5\frac{3}{4}$
	16	40	8.2	57	5
	17	40	8.0	90	6
	18	40	8.0	35	$3\frac{1}{4}$
	19	40	8.3	75	-
	20	40	9.0	95	5
	21	40	8.4	64	4
	22	40	10.2	73	$2\frac{3}{4}$
	23	40	7.3	100	4
MEANS		40	8.2	73.0	4.5

TABLE 3.

CARDIAC ASYSTOLE.

Series.	Exp. No.	Asystole at $T^{Ho}C$ Cool	Rewarm	Duration. mins.	Ventricular Fibrillation Temporary	Reversible	Irreversible
III	1	-	-		-	-	-
	2	12.3	26.5	108	-	-	-
	3	8.9	VF	-	-	C.Conv.	-
	4	14.6	VF	-	-	C.Conv.	-
	5	11.7	15.7	93	-	-	-
	6	11.0	12.5	39	-	-	-
	7	8.7	11.8	36	+(C)	-	-
MEANS		11.2	16.6	69	1	2	0
IV	1	16.2	14.0	29	-	-	-
	2	VF	VF	-	+(C+R)	-	-
	3	18.0	13.5	35	-	-	-
	4	14.5	14.8	25	-	-	-
	5	12.0	14.9	32	-	-	-
	6	13.5	13.8	23	+(C)	-	-
	7	14.2	13.9	29	-	-	-
	8	12.9	14.7	24	-	-	-
	9	13.5	15.8	21	-	-	-
	10	14.1	14.9	25	-	-	-
	11	13.5	16.4	26	-	-	-
	12	12.7	15.2	25	-	-	-
MEANS		14.1	14.7	26.7	2	0	0
	13	14.5	VF	-	-	K.Conv.	-
	14	13.5	15.0	22	-	-	-
	15	14.4	13.9	16	-	-	-
	16	12.4	14.7	19	-	-	-
	17	11.7	14.2	19	-	-	-
	18	13.0	16.4	22	-	-	-
	19	14.0	13.8	18	-	-	-
	20	14.4	13.2	14	-	-	-
MEANS		13.5	14.6	18.6	0	1	0

TABLE 3. continued.

CARDIAC ASYSTOLE.

Series.	Exp. No.	Asystole at $T^{Ho}C$ Cool	Rewarm	Duration. mins.	Ventricular Fibrillation Temporary	Reversible	Irreversible
V	1	8.5	-	-	-	-	+
	2	11.4	22.9	108	+(C)	-	-
	3	-	-	-	-	-	-
	4	13.1	-	-	-	-	+
	5	12.8	-	-	-	-	+
	6	11.5	VF	-	-	+ (K)	-
MEANS		11.5	22.9	108	1	1	3
VI	1	9.0	12.0	47	-	-	-
	2	14.3	15.8	54	-	-	-
	3	13.2	12.9	48	-	-	-
	4	13.5	16.8	63	-	-	-
	5	19.8	11.0	98	-	-	-
	6	15.8	16.0	94	+(Riv)	-	-
	7	13.5	16.0	85	-	-	-
	8	13.8	14.7	68	-	-	-
	9	14.5	15.9	55	-	-	-
	10	12.6	14.5	83	-	-	-
	11	12.5	13.9	51	-	-	-
	12	15.1	16.7	63	-	-	-
MEANS		14.0	14.7	67.4	1	0	0
	13	12.5	15.2	49	-	-	-
	14	13.2	14.7	50	-	-	-
	15	12.1	16.3	54	-	-	-
	16	18.5	15.1	62	-	-	-
	17	19.8	14.0	49	-	-	-
	18	11.0	12.5	53	-	-	-
	19	13.8	14.5	66	-	-	-
	20	10.7	14.6	64	-	-	-
	21	16.0	13.9	61	-	-	-
	22	14.2	13.4	59	-	-	-
	23	10.6	13.2	59	-	-	-
MEANS		13.9	14.3	56.9	0	0	0

TABLE 4.

TEMPERATURES on COMPLETING COOLING and REWARMING.

Series.	Exp.	COOL. $T^{Ho}C$	COOL. $T^{Ro}C$	COOL. $T^{Mo}C$	REWARM. $T^{Ho}C$	REWARM. $T^{Ro}C$	REWARM. $T^{Mo}C$
III	1	17.0	20.4	-	31.7	30.3	-
	2	7.8	9.2	-	31.8	25.0	-
	3	6.0	8.7	-	33.0	28.1	-
	4	6.7	9.5	12.0	32.4	30.4	22.8
	5	4.9	6.0	9.9	35.2	33.0	20.2
	6	6.0	10.4	17.8	33.0	31.8	24.0
	7	5.8	9.5	15.3	33.0	30.5	18.7
MEANS		7.7	10.5	13.8	32.9	29.9	21.4
IV	1	8.0	18.0	23.0	33.0	26.5	26.5
	2	4.5	15.0	21.5	33.3	27.7	23.0
	3	12.0	18.4	20.7	33.2	26.3	26.0
	4	4.8	17.3	-	34.4	31.2	-
	5	6.3	17.9	-	34.3	25.6	-
	6	8.0	17.9	20.2	34.0	25.8	23.0
	7	9.5	15.8	-	34.0	23.3	-
	8	4.7	16.2	-	35.4	25.3	-
	9	10.5	15.9	23.5	32.7	31.5	26.5
	10	5.0	11.0	23.0	34.6	32.5	24.5
	11	7.2	16.8	-	36.0	30.5	-
	12	6.4	15.4	-	36.7	31.5	-
MEANS		7.2	16.3	22.0	34.3	28.1	26.6
	13	4.5	16.4	22.8	40.0	30.5	27.9
	14	3.6	17.0	26.4	40.0	36.9	32.0
	15	5.0	14.5	24.5	40.0	35.3	28.5
	16	5.0	16.5	24.0	40.0	35.2	28.0
	17	4.8	16.2	25.0	40.0	35.3	27.0
	18	4.0	18.0	-	40.0	31.0	-
	19	4.0	17.9	-	40.0	29.0	-
	20	4.6	11.8	18.4	40.0	33.2	26.5
MEANS		4.4	16.0	23.5	40.0	33.3	28.3

TABLE 4. continued.

TEMPERATURES on COMPLETING COOLING and REWARMING.

Series.	Exp.	COOL. $T^{Ho}C$	COOL. $T^{Ro}C$	COOL. $T^{Mo}C$	REWARM. $T^{Ho}C$	REWARM. $T^{Ro}C$	REWARM. $T^{Mo}C$
V	1	3.7	6.0	14.0	-	-	-
	2	4.8	12.3	18.8	32.3	24.9	22.3
	3	5.4	-	-	-	-	-
	4	6.0	8.3	-	31.0	25.0	-
	5	5.0	14.0	13.0	30.0	23.9	25.0
	6	3.7	14.5	14.5	35.0	26.7	23.5
MEAN		4.8	11.0	15.1	32.1	25.1	23.6
VI	1	3.6	11.8	20.6	40.0	37.5	25.7
	2	4.8	12.5	15.4	40.0	35.3	27.9
	3	4.2	10.2	16.7	40.0	38.9	28.0
	4	3.4	19.3	24.0	40.0	35.0	29.6
	5	4.2	5.7	9.4	40.0	34.9	26.6
	6	6.4	6.1	9.8	40.0	35.8	28.2
	7	4.3	10.2	15.6	40.0	40.0	34.6
	8	3.6	10.4	15.3	40.0	33.0	33.5
	9	4.8	7.6	-	40.0	37.5	-
	10	3.6	15.2	20.6	40.0	25.2	21.6
	11	4.8	12.3	18.5	40.0	36.0	31.4
	12	6.0	11.5	17.3	40.0	36.3	30.2
MEAN		4.5	11.1	15.3	40.0	35.5	26.4
	13	4.8	11.6	22.0	40.0	37.2	33.4
	14	5.0	15.0	24.5	40.0	36.7	35.3
	15	4.6	12.7	18.7	40.0	39.1	31.4
	16	5.0	10.5	25.4	40.0	40.0	34.2
	17	5.0	13.0	17.7	40.0	37.2	34.0
	18	4.6	9.8	16.0	40.0	40.0	34.2
	19	3.2	7.3	-	40.0	37.5	32.8
	20	4.6	13.0	17.5	40.0	38.6	38.2
	21	4.0	12.2	16.6	40.0	34.6	30.0
	22	3.8	7.2	-	40.0	37.8	-
	23	4.5	11.5	22.6	40.0	40.0	36.9
MEAN		4.5	11.3	16.5	40.0	38.0	34.5

TABLE 5.

TEMPERATURES at BEGINNING (1) and END (2) of TOTAL CIRCULATORY ARREST.

Series.	Exp. No.	Period of Arrest min.	T_{H1} °C	T_{H2} °C	T_{R1} °C	T_{R2} °C	T_{M1} °C	T_{M2} °C	T_{B1} °C	T_{B2} °C
V.	1	30	3.7	6.2	6.0	10.5	14.0	13.3	-	-
	2	20	4.8	6.0	12.3	13.2	18.8	18.4	-	-
	3	16 hr.	3.4							
	4	20	6.0	8.9	8.3	11.5	-	-	-	-
	5	60	5.0	8.5	14.0	14.8	13.0	12.2	-	-
	6	60	3.7	8.0	14.5	17.8	14.5	16.5	-	-
MEAN		38	4.8	7.5	11.0	13.6	15.1	15.1		
VI.	1	30	3.6	7.2	11.8	15.6	20.6	18.9	-	-
	2	30	4.8	7.6	12.5	13.9	15.4	15.2	-	-
	3	31	4.2	7.3	10.2	12.8	16.7	17.1	-	-
	4	30	3.4	7.2	19.3	20.2	24.0	24.8	10.0	13.5
	5	30	4.2	4.8	5.7	9.3	9.4	12.5	4.4	5.0
	6	30	6.4	9.6	6.1	8.7	9.8	11.3	-	-
	7	30	4.3	8.5	10.2	13.5	15.6	16.4	-	-
	8	30	3.6	3.8	10.4	11.9	15.3	18.5	-	-
	9	30	4.8	12.0	7.6	14.5	-	-	-	-
	10	30	3.6	6.8	15.2	16.0	20.6	16.8	-	-
	11	30	4.8	7.5	12.3	14.7	18.5	18.7	-	-
	12	30	6.0	8.4	11.5	12.1	17.3	19.8	-	-
MEAN		30	4.5	7.5	11.1	13.6	15.3	15.8	7.2	9.3
	13	30	4.8	8.0	11.6	17.4	22.0	21.6	-	-
	14	30	5.0	10.4	15.0	15.0	24.5	22.6	-	-
	15	30	4.6	9.2	12.7	14.9	18.7	20.1		
	16	30	5.0	9.8	10.5	13.4	25.4	24.1	-	-
	17	30	5.0	9.2	13.0	15.0	17.7	19.4	-	-
	18	45	4.6	8.3	9.8	15.4	16.0	20.2	-	-
	19	45	3.2	6.4	7.3	10.6	-	-	-	-
	20	45	4.6	10.8	13.0	14.7	17.5	19.6	-	-
	21	45	4.0	8.8	12.2	15.0	16.6	17.1	-	-
	22	45	3.8	6.7	7.2	10.4	-	-	-	-
	23	45	4.5	7.7	11.5	18.9	22.6	22.0	-	-
MEAN		38.2	4.5	8.9	11.3	15.0	16.5	20.6		

TABLE 6.

ISOTONIC $NaHCO_3$ INFUSION DURING PERFUSION.

Series.	Exp. No.	Weight. Kgs.	Cool. mls.	Rewarm. mls.	Total. mls.	Lowest pH Observed.
VI	13	10	150	150	300	7.25
	14	16	150	200	350	7.28
	15	14.5	150	200	350	7.32
	16	12.5	150	150	300	7.26
	17	14	150	200	350	7.28
	18	14	200	200	400	7.29
	19	13.5	200	150	350	7.31
	20	12.5	150	200	350	7.27
	21	15	150	175	325	7.32
	22	17	150	200	350	7.29
	23	13.5	200	350	550	7.30
MEANS		13.9	163.6	197.7	361.4	7.29

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WESTERN REGIONAL HOSPITAL BOARD

Telephone:
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Ref: FC/MB

4th May, 1960.

Dear Sir/Madam,

Consultant Anaesthetist, Glasgow Royal Infirmary
Whole-time or Maximum Part-time Sessions

In connection with the above appointment the following candidates have been selected for interview:-

Dr. W.S. Dykes, M.B., Ch.B., D.A., F.F.A.R.C.S.
Dr. K.B. Holloway, M.B., Ch.B., D.A., F.F.A.R.C.S.
Dr. W.W. Jones, M.B., B.Ch., B.A.O., F.F.A.R.C.S., D.A.
Dr. B. Kay, M.B., Ch.B., D.A., F.F.A.R.C.S.
Dr. J.E. Norman, M.B., Ch.B., D.A., F.F.A.R.C.S.

A meeting of the Advisory Appointments Committee will be held in the Offices of the Regional Board, 351 Sauchiehall Street, Glasgow, C.2, on Thursday, 12th May, 1960, at 2.30 p.m., to interview the candidates listed above and to place them in order of suitability for the appointment.

I trust it will be convenient for you to attend.

Yours faithfully,

Secretary.

Representing the Regional Board:

Mr. A.H. Sangster (Convener)
Miss E.G. Manners

Representing the Board of Management:

✓ Dr. A.C. Forrester
Mr. W. Patrick

Representing the ~~National Panel of Specialists~~:

Dr. D. Keir Fisher
Dr. W.M. Shearer

Representing the University of Glasgow:

Dr. A.C. Forrester
Professor W.A. Mackey
Professor C.F.W. Illingworth
Professor W.J.B. Riddell
Professor T. Symington
Professor J.N. Davidson