# TECHNIQUES OF EXTRACORPOREAL CIRCULATION

by

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Preface:

This thesis was prepared when I was engaged in a research project in the Experimental Surgical Laboratory at McGill University, under the direction of Doctor David R. Murphy, Surgeon-in-Chief at the Montreal Children's Hospital. Other members of our research group were Doctor Gordon Karn, Doctor E. Dowd and Doctor G. Bisson from the Montreal Children's Hospital.

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# CHAPTER I

## INTRODUCTION

The past decade has seen a remarkable world-wide development in the field of thoracic surgery. Following the lead of surgeons in the United States, the United Kingdom and Sweden, and the original pioneering contributions made by our own Canadian surgeons, namely Doctor Edward Archibald, Dr. William Mustard and Doctor W.G. Bigelow, rapid strides are being made not only in the scope of thoracic surgery, generally, but, more specifically, in the advancement of cardiac surgery.

The measure of success achieved by efforts to correct congenital cardiac anomalies by indirect surgical procedures has served to encourage world-wide research in developing techniques by which cardiac defects may be corrected by direct methods under direct vision.

In order to facilitate such surgical procedures an artificial means for the maintenance of circulation and oxygenation of the blood was mandatory.

This experimental project is concerned with the study of the various techniques of extracorporeal circulation that have been developed elsewhere, in order to evaluate and become proficient in the use of a suitable heart-lung apparatus to be applied clinically.

After review of the literature it became obvious that the pumping mechanism was not as great a problem as was oxygenation of blood without causing undue alteration of constituents of blood. Three main techniques of extracorporeal circulation presented possibilities for clinical application; namely, (1) controlled cross-circulation, (2) the use of a heterogenous biological lung oxygenator and pump and (3) artificial oxygenation of blood with a pump.

This investigation was confined to these three techniques of extracorporeal circulation.

# CHAPTER II

## HISTORICAL SURVEY

Le Gallois (122) in 1812 made the following statement "If one could substitute for the heart a kind of injection of arterial blood either naturally or artificially made one would succeed easily in maintaining alive indefinitely any part of the body whatsoever".

The first recorded description of a heart-lung preparation was made by Martin (139) in 1881. Isolated animal lungs, artifically respired were used to provide oxygenated blood for a working animal heart.

In 1903 Brodie (20) described an artificial oxygenator. Air was bubbled through a perfusate of Locke's solution and Ringer's solution. Brodie was able to maintain an isolated rabbit's heart for four hours with this oxygenator. A cam driven pump and a glass wool filter were included in this apparatus. The author performed further experiments using blood for perfusion. It was noted that oedema occurred in most organs perfused, and notably lungs, when the perfused blood was diluted with saline, but no oedema occurred when blood alone was used. It was also reported that oedema was less likely to occur if the perfusate was supplied by pulsating rather than constant pressure.

One of the first successful open cardiac operations was performed experimentally on a dog by Haecker (76) in 1907. The azygos vein was ligated, and the superior and inferior venae cavae were temporarily occluded. Through an incision in the right ventricle a defect was created in the interventricular septum. The animal survived the operation. It was noted in further experiments that the cardiac function was better maintained when the azygos vein remained patent throughout the operation.

## Cross-Circulation

The technique of using an entire donor animal for the purpose of oxygenation and perfusion of the blood of a second animal, or an isolated portion thereof, is known as cross-circulation. An extracorporeal circuit is necessary to convey oxygenated blood from the arterial system of the donor animal to the arterial system of the recipient animal, and the venous blood from the venous system of the patient animal to the venous system of the donor animal.

Early experiments by Houssay and Hug in 1928 were directed toward the maintenance of life in an isolated portion of an animal by means of cross-circulation with a second intact animal. By means of cannulae a carotid artery and jugular vein of an isolated dog's head were anastomosed with a carotid artery and jugular vein of an intact donor dog. Corneal reflexes were noted to return in the isolated head after five minutes perfusion but did not persist after eleven minutes perfusion.

The same authors also cross-circulated an isolated heart-lung preparation with a donor dog. Artificial respiration was applied to the isolated lung. The authors were able to maintain the heart beat in the isolated preparation for the duration of the experiment.

The perfusion of an entire animal by cross-circulation with a homologous donor animal was reported by Kerr et al (110) in 1951. A fenestrated catheter was introduced into the jugular vein of the patient animal and advanced so that its terminal portion was situated in the inferior vena cava. This catheter was connected to the venous line of the extracorporeal circuit. The arterial line of the extracorporeal circuit was connected to a catheter which had been advanced into the descending aorta by way of the

femoral artery of the patient animal. During perfusion the heart and lungs of the patient animal were excluded from the circulation by temporary occlusion of the superior and inferior venae cavae and descending aorta. Cardiotomy was successfully performed. However, upon release of the ligatures about the superior and inferior venae cavae sudden dilatation of the heart was noted.

In an effort to ascertain the minimal flow of blood that would be sufficient to adequately oxygenate the myocardium and cerebral centers Andreasen and Watson (3) produced experimental evidence that the maintenance of a small flow of blood through the azygos vein with the venae cavae clamped was sufficient to maintain the brain and heart without detriment to full functional recovery for periods of at least thirty-five minutes. This was later to be referred to by other workers as "The azygos flow principle". In 1952 these same authors (4) stated that the measured flow of blood through the azygos vein prior to clamping the venae cavae was 18 c.c. per minute. Immediately after ligation of the superior vena cava the flow rate rose to 106 c.c. per minute. After ligation of the inferior vena cava as well the flow rate fell to 80 c.c. per minute. This figure related to the "azygos flow principle" cited in earlier experiments. A steady fall of flow rate of 18.5 c.c. was noted in each 20 minute interval. The authors reported that the minimal critical level for sustaining the heart in order to maintain reflexes in the patient animal was 150 c.c. per minute. The limit of period of safety for recovery was about 40 minutes.

In 1953 Andreasen and Watson (5) (6) introduced the term "controlled cross-circulation". An arterial and a venous pump were used to control the arterial and venous flow rates between the donor and blood

recipient animal. It was reported that the arterial input had to be carefully guaged so as to be as close as possible to the rate of venous return whilst remaining above a rate known to be the lowest at which myocardial function could be satisfactorily maintained. The optimum flow rate for the average dog ranged between 225 to 300 c.c. per minute delivered as aortic flow at the coronary ostia.

At lower flow rates the heart tended to overdistend after release of the venae cavae. Even with higher flow rates gradual release of the inferior vena cava was important in order to avoid overdilatation of the heart. Ventricular fibrillation was also noted to occur more frequently during perfusion when lower flow rates were used.

Cohen and Lillehei (32) in 1954 reported that the "azygos flow" ranged between 8 to 14 c.c. per kilogram per minute. This was approximately one-tenth of the basal cardiac output of 165 c.c. per kilogram per minute. Dogs were successfully maintained for 30 minutes or longer, with arrest of circulation through the heart and lungs, on this amount of blood flow. No damage could be detected to the vital organs of animals maintained with a blood flow of far less magnitude than those which they normally receive.

Further experiments revealed that for open intracardiac surgery, performed with the technique of controlled cross-circulation, flow rates 3 to 5 1/2 times the "azygos flow" offered the patient animal a greater margin of safety, even though vital functions could be maintained with flow rates approximating the "azygos flow". Warden et al (199) (200) in 1954 reported that optimum flow rates appeared to be between 30 and 50 per cent of the basal cardiac output of the patient animal.

These same authors reported interesting biological changes which occurred during cross-circulation. The patients' arterial blood oxygen content rose and the venous blood oxygen content fell. This phenomenon represented an increase in the recipients' coefficient of oxygen utilization. This appeared to be associated with a mild degree of acidosis which appeared to augment dissociation of oxyhemoglobin. Observations on clinical applications of controlled cross-circulation were reported by Lillehei (129) in 1955.

Tygon (180) plastic tubing was used for the extracorporeal circuit. This was primed with 5 per cent glucose in distilled water or with normal saline prior to perfusion. Because the tubing was relatively inexpensive it was discarded at the conclusion of each operation.

Perfusion flow rates of 25 to 40 c.c. per kilogram per minute were used.

Polyethylene catheters were inserted into the superior vena cava and inferior vena cava by means of small incisions placed in the wall of the right auricle and controlled by purse string sutures. The systemic arterial catheter was introduced into the ascending aorta of the patient through the proximal end of a divided subclavian artery.

The donor was prepared by catheterization of a superficial femoral artery. The catheter was advanced so that its tip was situated in the abdominal aorta. The venous catheter was advanced through the saphenous vein so that its tip was placed in the inferior vena cava.

During perfusion an increase in the donor's respiratory minute volume was necessary to maintain his alveolar $pCO_2$ within normal limits as monitored by a portable mass gas spectrometer during the period of perfusion.

The donor's aortic and vena caval pressures tended to rise during the perfusion with a peak at 28 minutes perfusion. The recipient's aortic pressure tended to fall although his vena caval pressure tended to rise. All blood pressures rapidly returned to normal at the conclusion of the procedure.

Of thirty-two patients who underwent intracardiac operations with the aid of controlled cross-circulation there were twenty who survived.

## Biological Lung Oxygenation

The earliest experiments with autogenous lung oxygenation were reported by Starling (186) in 1912, Gibbs (65) in 1930 and Hemingway (80) in 1931. Starling described a heart-lung preparation utilizing a cat's own lung for oxygenation. Hemingway perfused an isolated kidney by means of an extracorporeal circuit and a pump. The animals own lung was used as an oxygenator. Gibbs was able to maintain an entire animal utilizing the subjects own lung for oxygenation while the heart was temporarily excluded from the circulation by means of ligatures placed about the superior and inferior venae cavae and the azygos vein. Sirak, Ellison and Zollinger (183) reported experiments in which cardiotomy into an empty left ventricle was performed with the use of an extracorporeal circuit and autogenous lung oxygenation.

Successful maintenance of the circulation of an entire animal with the use of an isolated homologous lung for oxygenation and a pump for perfusion was first reported by Barcroft (7) in 1933. The right ventricle was opened in ten animals with the aid of homologous lung oxygenation by Mustard and Chute (149) in 1951. It was noted by Gerst el al. (57) that cyanotic blood became fully oxygenated during a single passage through an isolated homologous lung. Perfusion was successfully maintained for three hours with homologous lung oxygenation by Potts et al (163) in 1952. In order to preclude the development of oedema in the donor lung it was found that freshly resected lung tissue must be used, and also that positive pressure respiration must not be too vigorous.

Wèsalowski and Welch (205) in 1952 described an apparatus utilizing rubber and glass tubing. Two pumps, a reservoir, lucite valves, and a T-shaped lucite pump chamber which produced positive-negative pressure by acting as an air piston were included in the apparatus. Two filters of fine mesh monel metal with spaces of 200 by 300 (microns) were incorporated in the extracorporeal circuit. Autogenous lung was used for oxygenation. Positive pressure respiration at 10 to 12 cm. water endotracheal pressure was used. Perfusion time was 2 hours. Oedema of the donor lung was a major complication in early experiments.

One experiment of heterogenous lung oxygenation was reported. A donor sheep lung was used to oxygenate a patient dog with survival of the animal.

Heart-lung dissection en bloc with insertion of the pulmonary artery catheter by way of the auricular appendage was recommended. In this way the introduction of air emboli into the vascular system of the donor dog was eliminated.

A series of 55 experiments with total cardiac bypass for experimental intracardiac surgery utilizing autogenous lung oxygenation was reported by Cohen and Lillehei (31) in 1953. Blood flow rates of 8 to 14 c.c. per kilogram per minute were used. Measurement of pH and plasma carbon dioxide content revealed a slight metabolic acidosis during the experiments. The blood $pCO_2$ content was only slightly elevated. After once passing through the pulmonary circuit the blood showed 100 per cent oxygen saturation. The survival rate was 90.9 per cent in a series of 55 animals with exclusion of the heart for a 30 minute period.

The first clinical operation with the use of monkey lung for oxygenation was performed on an infant by Mustard and Sirek (151) in 1954. Difficulty in maintaining an adequate venous return from the patient was reported.

Cohen, Warden and Lillehei (33) in 1954 reported on the physiologic and metabolic changes when using an autogenous lobe for oxygenation. The systemic blood pressure during occlusion of the venae cavae ranged between 30 and 40 mm. mercury, and returned to control levels after release of the venae cavae. Hemolysis after 30 minutes perfusion was considered minimal. Plasma hemoglobin levels between 35 and 70 mgm. per cent were reported. It was claimed that values in excess of 200 mgm. per cent were necessary to produce renal damage. Heparin in a dosage of 0.75 mgm. per pound body weight was used. Troublesome post-operative oozing of blood from cut surfaces in these experiments was rare, and when it did occur it was readily controlled by a single intravenous dose of 50 mgm. protamine sulfate.

A moderate degree of hemoconcentration 5 to 20 per cent over control levels was noted. Renal function studies were all within normal limits.

Arterial blood oxygen contents were all between 90 and 100 per cent during perfusion. A small drop in pH of the blood was noted. A rise in lactic acid was reported. The principal portion of the acidosis appeared to be the accumulation of acid metabolites which monopolized the blood buffers. Liver function tests were all within normal levels.

In 1955 Campbell, Crisp and Brown (22) reported a comparative series with autogenous and homologous lobe oxygenation. With blood flow rates of 32 to 38 c.c. per kilogram per minute the arterial pressure during perfusion was registered at about 75 mm. mercury. Intermittent positive pressure ventilation of the donor lung with 100 per cent oxygen at 14 to 16 cm. water pressure at the rate of 12 to 18 cycles per minute, was used.

A double Sigmamotor pump (180) was used to propel the blood in the extracorporeal circuit. The pump consisted of an electric motor which set in motion two pump heads. Rubber tubing 10/16 inches external diameter traversed each pump head. A finger-like action of metal rods propelled the blood forward in a pulsatile wave by applying external pressure in sequence to the tubing within the pump head.

A depulsator in the extracorporeal system was found to be most important. This was placed between the venous pump and the donor lung. The donor lung showed considerably less weight gain after perfusion when the depulsator was used in the system.

The extracorporeal system consisted of Tygon tubing, a methyl methacrylate collecting chamber in which the donor lung was suspended, rubber tubing within the Sigmamotor pump heads and gum rubber tubing within the depulsator. Size #12 and #14 French plastic catheters were used to cannulate the vessels.

Heparin, 1 mg. per kilogram body weight was given intravenously pre-operatively. At the conclusion of the operation, protamine sulfate 1 mg. per kilogram, diluted in 100 c.c. normal saline, was administered intravenously over a period of 5 to 10 minutes.

Careful monitoring of the arterial and venous flow rates was essential during perfusion. The level of blood in the reservoir was used as a guide.

In each series of 10 experiments there were 5 long term survivals.

## Artificial Oxygenation of Blood

### Early Experiments:

The first successful attempt at artificial oxygenation of blood was reported by Zeller (214) in 1908, who noted that oxygenation of blood could be achieved in vitro by bubbling oxygen through blood.

Chemical oxygenation was reported as early as 1910 by Læwen and Sievers (121) who experimented with sodium perborate as the oxidizing agent.

Hooker (851) in 1910 first described an artificial oxygenator with an extracorporeal circuit. Blood was pumped by means of a motor driven piston. A cam and sliding carriage altered the volume per minute flow of blood. Oxygenation was achieved by bubbling either oxygen or an oxygen-carbon dioxide mixture through defibrinated blood in a glass reservoir. The gas escaped through a vent at the top. Blood was drained at the bottom of the reservoir. This apparatus produced a pulsatile flow which allowed alteration of magnitude of pulse pressure. An isolated dog kidney was perfused. A correlation was noted between the magnitude of the pulse pressure, the rate of blood flow and the amount of urinary filtration formed.

The first oxygenator in which a blood film was exposed to an atmosphere of oxygen was constructed by Richards and Drinker (170) in 1915. In this apparatus the blood was filmed over a silk screen exposed to an atmosphere of oxygen. A pump and extracorporeal circuit were part of the apparatus. A blood flow rate of 50 cc. per minute was reported. The apparatus was used for perfusion of isolated organs.

Isolated organ perfusion with artificial oxygenation was again reported by Hooker (86) in 1915. For purposes of oxygenation blood was allowed to form a film over an inverted revolving bell jar while exposed to

an atmosphere of oxygen. The medulla of a dog was perfused for two hours with the cardiac and respiratory centers remaining active.

Drinker et al. (45), in 1922, reported successful perfusion of the tibia of a dog with an artificial oxygenator improved from the original apparatus described in 1915.

In 1928 Dale and Schuster (37) described an air-piston pump which formed the basis of many present day heart pumps.

## Attempts at Artificial Oxygenation of Blood by Intravenous Administration of Various Substances

Lighty et al. (126), in 1932, and Degowin et al (39), in 1938, attempted oxygenation of blood by intravenous administration of hemoglobin. Lighty noted hemaglobinuria in animals following injection of 124 to 210 mg. of hemoglobin per kilogram body weight. Degowin reported that, upon transfusion of canine hemoglobin into dogs, death from renal insufficiency occurred when the urine was acid, but not when it was alkaline. Autopsy specimens showed tubular obstruction and necrosis.

Efforts to oxygenate blood in vivo by intravenous administration of oxygen were reported by Singh (182) in 1935, Dick (41) in 1939, Ziegler (215) in 1941, Goodwin and Harmel (72) in 1949 and Lary (120) in 1951. Dick noted pulmonary emboli accompanied by anoxemia almost immediately after the administration of oxygen into the femoral vein of dogs. This was accompanied by an increase of pressure within the right auricle. Ziegler reported the use of intravenous administration of oxygen clinically at the rate of 200 c.c. to 600 c.c. per hour. Oxygen emboli in the blood stream were noted. Goodwin and Hormel experimented with intravenous oxygen and helium for artificial oxygenation of blood. Lary reported the addition of a small amount of wetting agent to the oxygen and then passing it through a filter paper to reduce the size of the bubbles before injecting it intravenously into dogs. There were 5 long term survivals following intravenous oxygen administration for periods up to 50 minutes.

Siderova (179) in 1944 reported experiments in which hydrogen peroxide was used for chemical oxygenation of blood.

## Blood Film in Contact with Oxygen

The principle of oxygenation by exposure of a thin film of blood to an atmosphere of oxygen has intrigued numerous workers. An almost infinite variety of oxygenators constructed on this principle have been described.

De Burgh Daly and Thorpe (38) in 1933 described an apparatus consisting of three tall revolving glass cylinders and three horizontal revolving discs arranged concentrically. The blood was allowed to form a film on the concentric cylinders for exposure to an atmosphere of oxygen.

A tier of horizontal revolving aluminum plates formed the surface for the blood film in an oxygenator described by Evans et al (51) in 1934. Some difficulty with frothing of blood was reported. This was highly undesirable since air emboli tended to enter the arterial line and so produce fatal cerebral and coronary air emboli.

In order to eliminate frothing of blood Cruickshank (36) in 1934 used a rotating spiral sheet of nickel plated copper as the surface for the blood film.

Gibbon (58), (60), (61) used a revolving steel cylinder as the surface for the blood film which was introduced at the top of the cylinder. Oxygen was introduced through an inner tube at the bottom of the cylinder. This apparatus achieved 98 per cent oxygen saturation of the blood.

A vertical rotating plate was described by Kolff (115) in 1946 as the surface for the blood film exposed to oxygen.

The inner wall of spiral tubing was used by Jongbloed (101), (102) as the surface for a blood film.

Karlson et al. (108) in 1949, attempted to follow the lead of Kolff (116) and interposed a thin membrane between the blood and oxygen atmosphere. Cellulose sausage casing was used. This presented too great a barrier to the diffusion of oxygen to make the Kolff apparatus an efficient oxygenator. He later described an apparatus in which the oxygenator consisted of 8 vertically revolving concentric cylinders and a funnel to deliver blood into a cup shaped reservoir.

Survival of a dog following a 2 hour perfusion with the aid of an artificial oxygenator was reported by Jongbloed (102) in 1949. The oxygenator consisted of plastic tubing revolved about a central axis. The blood film was allowed to form on the inner wall of the tubing.

A wire screen was first used by Stokes and Flick (188) in 1950 to line the inner surface of a vertical metal cylinder oxygenator. By thus creating turbulence in the blood film an attempt was made to increase the capacity of introduction of oxygen into the blood.

The first screen oxygenator was described in 1951 by Miller, Gibbon et al. (145). Six stainless steel screens were suspended in parallel from a distributing chamber and enclosed in a clear plastic case. The glass joints in the apparatus were siliconized with DC 200, manufactured by Dow Corning Corporation of Midland, Michigan. Tygon plastic tubing was used for the extracorporeal circuit. A 5 per cent carbon dioxide - 95 per cent oxygen mixture was used for oxygenation. Blood flow rates up to 2000 c.c. per minute were used on patient dogs. At the conclusion of the operation protamine sulfate in dosage equal to the heparin given was administered intravenously over a 20 minute period. In a series of 21 experiments 6 survivals were reported.

An automatic device which maintained the blood pH within physiological limits was described by Gibbon (62) in 1951. It functioned by the addition or exclusion of carbon dioxide to the oxygen atmosphere in contact with the blood film.

An apparatus in which a system of jets filmed blood on several screen discs as they rotated slowly on a horizontal axis was described by Dennis et al (40) in 1951. A flowmeter was used in the extracorporeal circuit.

Gimble and Engelberg (69) in 1952 described an artificial oxygenator in which blood was distributed in a film over a column of large bubble foam. The oxygenated blood was collected into the blood pool below the foam area. There was apparently no problem with foaming in the extracorporeal circuit in experimental use of this apparatus.

Waud (202) in 1952, was able to control the size of the aggregation of bubbles by the rate of oxygen flow. This was a significant contribution from the standpoint of efficiency of oxygenation of the blood in the bubbling chamber.

Melrose and Aird (143) in 1953 noted that the optimum time of exposure of the red blood cell to oxygen was 0.5 seconds. They described an oxygenator in which a rotating cylinder was set at a slight angle to the horizontal allowing the blood to travel within it from the top downward and to spread over blades projecting into the lumen of the cylinder in the shape of a helix.

Polyvinylchloride tubing, treated with Dow Corning dimethyldichlorosilane within the lumen, was used in the extracorporeal circuit. The

authors reported that polyethylene tubing served just as well as polyvinyl-chloride tubing.

Melrose et al. (142) in 1953 reported that animals were successfully perfused for one hour at blood flow rates varying from 50 to 1000 c.c. per minute.

Helmsworth et al. (79) in 1953 described a filter of 325 mesh stainless steel screens with a baked silicone coating to be used between the pumping chamber and the animal in the arterial line.

Gibbon (64) in 1954 added a third pump to the oxygenator described earlier. Its purpose was to avoid accumulation of blood on the screens of the oxygenator. This pump drew blood from the bottom of the oxygenator chamber and also from the venous tubing. The flow from this pump was always greater than the vena caval flow. This pump operated at a fixed rate during perfusion. A suction chamber between the venal cavae and the pump on the venous side was added for smoother venous flow. A Cuvette oximeter was used for blood oxygen determination.

Donald et al. (43) in 1955 reported that the mixed venous oxygen saturation was maintained at relatively normal levels indicating adequate blood flow into the tissues.

Jones et al. (100) in 1955 reported further improvements in the Mayo Clinic oxygenator. Fourteen wire mesh screens each 12 by 18 inches were enclosed in a lucite case. The number of screens used varied with the expected volume of flow, and space blocks were used to reduce the volume when a small number of screens were required.

The blood entered at the top of each screen through a series of 0.006 inch carefully machined polished slats in the stainless steel floor of the upper oxygenator reservoir.

The lower oxygenator reservoir contained a removable lucite block which served to hold the free ends of the screens, and also helped to reduce the volume of the chamber. This chamber served as an outlet for oxygenated blood. The screens were wet with normal saline prior to perfusion.

Melrose (144) in 1955 reported the use of pumps which were capable of circulating 6 liters per minute. A pulsatile flow was obtained by a squeezing action of two metal plates on a straight plastic tube. The plates were operated by a cam shaft which imparted an undulating movement. Hemolysis of only 2 mgm. per cent after 2 hours perfusion was reported.

## Mechanical Mixing of Blood and Oxygen

The principle of foaming blood as a means of oxygenation, with subsequent defoaming, forms the basis of many present day artificial oxygenators.

An attempt to inject blood and oxygen under pressure through small tipped openings against the sides of a spherical glass bulb was made by Von Euler and Heymans (49) in 1932. The apparatus accommodated blood flow rates of 250 c.c. per minute.

Isolated organ perfusion with the aid of oxygenation by mechanical mixing of blood and oxygen was carried out by Thomas (190) in 1948. In early experiments blood was dripped through an atmosphere of oxygen. Subsequently, oxygen was bubbled through blood to achieve oxygenation.

Clark, Gollan and Gupta (27), in 1950, described an artificial oxygenator based on the principle of mechanical mixing of blood and oxygen. Oxygen was bubbled through blood. This was found to be a very rapid and efficient procedure for saturation of hemoglobin. In this apparatus the oxygen was dispersed in blood in the form of tiny bubbles, produced by passing the gas through a fretted glass disc or a porcelain bacteriological filter. The blood was made to swirl rapidly in the oxygenator chamber as the oxygen bubbles were dispersed through it. The oxygenator was humidified before it entered the oxygenator chamber. The rate of oxygen flow was monitored to obtain optimum oxygenation without excessive gas flow.

After oxygenation, which was nearly immediate, the excess gas was released by passing the blood over a surface coated with methylsiloxane resin, also known as anafoam and sold commercially as DC antifoam

A, manufactured by the Dow Corning Corporation, Midland, Michigan, U.S.A. The anafoam was coated on glass beads or fine glass rods set in a defoaming chamber.

The defoamed blood entered a reservoir which served also as a bubble trap. A filter of fine mesh glass cloth was placed in the arterial portion of the circuit.

Two pumps were used in the circuit, one in the arterial part, and the other in the venous part of the flexible polyethylene bottles which were mechanically alternately compressed and expanded.

Polyethylene tubing was used for the extracorporeal circuit.

All glass parts in the apparatus with the exception of the perforated plate were coated with silicone resin.

The apparatus was used for perfusion experiments in dogs with exclusion of the heart from the circulation. The venous blood was drained by means of a catheter inserted into the jugular vein and its tip advanced into the inferior vena cava. The catheter contained two sets of perforations to allow simultaneous drainage from the superior and inverior venae cavae. The oxygenated blood was returned to the patient animal by way of the femoral artery.

The arterial blood oxygen saturation was greater than 95 per cent. Comparatively high plasma hemoglobin levels up to 400 mg. per cent were recorded after the procedure was completed.

A similar principle was reported by Clowes (28). By the use of slight negative pressure, 1 cm. mercury, the oxygenated blood was drawn into a reservoir in which the bubbles and foam were allowed to rise to the surface. Modified Dale Schuster pumps were used at blood flow rates cal-

culated to maintain normal cardiac output. Oxygen saturation of the blood above 88 per cent was reported. It was noted that the blood pH could be raised by rapid ventilation of the lungs of the patient dog.

Gollan et al.(71), in 1952, reported experiments in which the pump oxygenator was used to secure rapid changes in body temperature, thus combining extracorporeal artificial oxygenation with hypothermia.

Dogliotti et al.(42), in 1954, described an artificial oxygenator in which a large candle of porous porcelain was used to produce a micro bubble mist. The candle-shaped porcelain inserted into a cylinder of an internal diameter 6 mm. greater than the diameter of the candle. Blood was introduced from above into the 3 mm. space between the candle and the cylinder. Oxygen was introduced from below and allowed to disperse through the porous porcelain candle. The apparatus produced no frothing. Oxygen saturation of more than 95 per cent was reported. The pH of the blood remained within the physiological range.

This apparatus was used clinically during three intra-cardiac operations with survival of the patients.

A centrifugal aerator for gas dispersion was described by Kusserow (119) in 1955. The oxygenator was a hollow cylinder of microporous porcelain, a bacteriological filter with a mean pore size of 5 m, which was placed in a cylindrical glass jacket. Oxygen was introduced through a side arm into the cylinder. A spiral ribbon of polyethylene within the lumen of the filter directed the blood flow in a swirling course. The centrifugal force directed the blood to the periphery while the bubbles remained in the center. The blood was forced through peripheral apertures into the glass receptacle. Waste gas was allowed to escape through a vent at the top of the chamber.

No anticoagulants were added to the blood and no foreign substances. Parts that came in contact with the blood could be sterilized by autoclaving.

In experiments performed a blood flow of more than 3 liters per minute was oxygenated and defoamed.

Lillehei et al. (131), in 1956 described a simple oxygenator which served as temporary replacement for the human lung.

The oxygenator had no moving parts. It was assembled entirely from commercially available pure polyvinyl food hose, and was sterilized by autoclaving. Because of its low cost it was disposed of after each clinical operation.

Oxygenation of venous blood was effected by direct introduction of 100 per cent oxygen in the form of large bubbles introduced into vertical plastic tubing. The oxygen entered the blood near the base of the mixing tube by way of 18 intravenous needles, size 22 standard, which had been inserted circumferentially through an ordinary rubber laboratory stopper. The bubbles were largely dissipated by momentary contact with a patent non-toxic silicone antifoam substance, DC antifoam A, Dow Corning Corporation, Midland, Michigan, which was sprayed or painted on the distal V-shaped portion of the walls of the mixing tube and the smaller plastic connecting tube of the apparatus. From the settling tube the arterialized blood entered a central collecting reservoir, an ordinary Kelly flask lined by a polyethylene bag. The oxygenated blood leaving the central reservoir was filtered through standard nylon blood filters, Baxter Laboratories, Incorporated, Morton Grove, Illinois.

The patients were heparinized with 1 1/2 mg. heparin per kilogram body weight. Heparinized blood was administered intravenously for blood replacement. Heparin, 18 mg. mixed with 50 c.c. of 5 per cent glucose was used for each 500 c.c. of fresh blood. The blood flow rates in clinical operations ranged from 172 c.c. per minute to 600 c.c. per minute. The patients' plasma hemoglobin levels, drawn immediately after perfusion, varied from 17 to 45 mg. per cent.

Seven patients operated on awakened immediately post-operatively, and there was no evidence of neurologic, hepatic or renal impairment of even a temporary nature. There was also no abnormal volume of hemorrhage observed in the post-operative interval.

TABLE 1

Experiments Performed

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 1 | Controlled Cross Circulation Between Two Dogs Cardiotomy Right Ventricle | 18 | | |
| 2 | Opening of Right Auricle Under Hypothermia Effected By External Body Cooling | | | Exclusion of heart and lungs 10 min. |
| 3 | Opening of Right Auricle Under Hypothermia Effected By External Body Cooling | | | Exclusion of heart and lungs 17 min. |
| 4 | Controlled Cross Circulation Between Two Dogs Cardiotomy Right Auricle | 8.5 | 7.5 | |
| 5 | Controlled Cross Circulation Creation of Inter Atrial Septal Defect And Repair | 14 | 5 | |
| 6 | Biological Homologous Lung Oxygenation Creation of Inter Atrial Septal Defect and Repair | 19.3 | 4 | |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 7 | Biological Homologous Lung Oxygenation Creation of Inter Atrial Septal Defect and Repair | 10 | 2.5 | |
| 8 | Biological Homologous Lung Oxygenation Creation and Repair of Inter Atrial Septal Defect | 26 | 13 | |
| 9 | Biological Homologous Lung Oxygenation Cardiotomy Right Auricle | 19 | 5 | |
| 10 | Biological Homologous Lung Oxygenation Cardiotomy Right Auricle | 13 | 3 | |
| 11 | Comparison of Perfusion Substances In Artificially Respirated Isolated Dog's Lungs Lobes | | | 1. Dextran 10% with Glucose 5%<br>2. Plasma<br>3. Autogenous Dog's Whole Blood<br>4. Normal Saline |
| 12 | Perfusion of Lobe of Dog Lung With Improved Drainage Technique | | | 1. Inverted Lobe Intermittent Negative Pressure Respiration<br>2. Inverted Lobe Intermittent Positive Pressure Respiration |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 13 | Biological Homologous Lobe Oxygenation Cardiotomy Right Ventricle | | | Inverted Lobe Intermittent Negative Pressure Respiration |
| 14 | Biological Homologous Lobe Oxygenation Cardiotomy Right Ventricle | 19 | 3 | |
| 15 | Biological Homologous Lobe Oxygenation Cardiotomy Right Ventricle | 12 | 5 | |
| 16 | Cardiotomy Right Ventricle Hypothermia Effected By Body Surface Cooling | | | Heart and Lungs Excluded From Circulation Ventricle Incised and Closed |
| 17 | Creation And Repair Of Inter Atrial Septal Defect Under Hypothermia Effected By Body Surface Cooling | | | |
| 18 | Correlation of Flow Rates And Pressures In Extra Corporial Circuit | | | Perfusion Substances 1. Water 2. Dextran 10% with Glucose 5% |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 19 | Measurement of Pulmonary Artery Pressure During Perfusion of Donor Lung | | | Method Devised |
| 20 | Perfusion of Isolated Dog Lung Biological Oxygenation of Whole Blood In Vitro Under Conditions of Temperature Control and Pressure Control in Pulmonary Artery of Donor Lung | | | Lung oxygenated at controlled pressure of 0 to 12 cm. H20 at rate of 14/min. Perfusion rates adjusted to maintain pulmonary artery press. at 18 to 20 mm. Hg. |
| 21 | Perfusion of Isolated Entire Lung Parenchyma of Dog With Dextran 10% and Glucose 5% Followed By Biological Oxygenation of Heporinized Autogenous Whole Blood In Vitro Under Conditions of Controlled Temperature and Perfusion Pressure | | | Temp. of Water Bath 42.5 to 48.25°C. Temp. of Blood 31.5 to 35°C. PA Press.mm.Hg. 6 to 29. Oxygen Press. mm. Hg. 20 to 40. Blood Flow Rate cc/min. per 200. |
| 22 | Biological Homologous Lung Oxygenation Cardiotomy Right Auricle | 29 | 6 | |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 23 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 30 | 3 | |
| 24 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 30 | 3 | |
| 25 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 30 | 4 | |
| 26 | Comparison Of Heinolytic Effect of Siliconed Glass and Plastic On Fresh Whole Human Blood | 30 | | Plasma Hemaglobin<br>1. Siliconed Glass Apparatus 0.661 gm.%<br>2. Plastic Apparatus 0.586% |
| 27 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 30 | 215 | Trans-sternal thoracotomy |
| 28 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 16 | 5 | |
| 29 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 31 | 4 | |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 30 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 30 | 5 | |
| 31 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 31 | 4 | Continuous Arterial Press. Tracing Measured In Descending Aorta of Patient Dog |
| 32 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 20 | 5 | Arterial Pressure Recorded |
| 33 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 20 | 2 | Arterial Pressure Recorded |
| 34 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | | | Arterial Pressure Tracing |
| 35 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | | | |
| 36 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | | | |
| 37 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | | | |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 38 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | | | |
| 39 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 20 | | |
| 40 | Biological Homologous Lung Oxygenation Cardiotomy Right Ventricle | 12 | 5 | |
| 41 | Artificial Oxygenation of Human Blood | | | |
| 42 | Artificial Oxygenation of Human Blood | | | |
| 43 | Artificial Oxygenation Cardiotomy Right Ventricle | 30 | | |
| 44 | Artificial Oxygenation Cardiotomy Right Ventricle | 30 | 5 | |
| 45 | Artificial Oxygenation Cardiotomy Right Ventricle | 30 | 1 | |
| 46 | Artificial Oxygenation | 60 | | |
| 47 | Artificial Oxygenation Creation and Repair of Inter Ventricular Septal Defect | 20 | | |

TABLE 1 Continued

| No. | Title | Per-fusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 48 | Artificial Oxygenation of Human Blood In Vitro | | | Studies Hemolysis p H Changes |
| 49 | Artificial Oxygenation Cardiotomy Right Ventricle | 12 | 3 | |
| 50 | Artificial Oxygenation Cardiotomy Right Ventricle | 36 | 5 | |
| 51 | Artificial Oxygenation of Human Blood In Vitro | 30 | | Fibrinogen studies |
| 52 | Artificial Oxygenation Cardiotomy Right Ventricle | 12 | | |
| 53 | Artificial Oxygenation Cardiotomy Right Ventricle | 20 | 3 | |
| 54 | Artificial Oxygenation Cardiotomy Right Auricle | | 10 | |
| 55 | Artificial Oxygenation Cardiotomy Right Ventricle | | | E.D.T.A. anticoagulant for donor blood |
| 56 | Artificial Oxygenation Cardiotomy Right Ventricle | 20 | | |

TABLE 1 Continued

| No. | Title | Perfusion Time Min. | Time Heart Open Min. | Description |
|---|---|---|---|---|
| 57 | Artificial Oxygenation of Dog's Blood in Vitro | | | Mechanical mixing of blood and oxygen with no bubbling Protamine heparin titration |
| 58 | Artificial Oxygenation Cardiotomy Right Ventricle | 30 | | |
| 59 | Artificial Oxygenation | 30 | | Anafoam diluted in ether |
| 60 | Effect of Heparin And Protamine In Various Dilutions On the Arterial Blood Pressure of Anesthetized Dogs | | | |
| 61 | Artificial Oxygenation | 30 | | |
| 62 | Artificial Oxygenation Cardiotomy Right Ventricle | 30 | | |

# CHAPTER III

## Cross-Circulation Experiments

Materials:

A double Sigmamotor pump (180) model T-63 was used. With this apparatus the flow rates of each pump head were individually adjustable. One electric motor served both pump heads. The pump functioned by progressive finger-like pressure of vertical metal rods upon rubber tubing placed within the pump head.

Tygon (180) plastic tubing, 3/16 inch internal diameter, was used for the extracorporeal circuit. Rubber tubing, 1/2 inch internal diameter, was used for the part of the circuit inside the pump heads. This was for a two fold purpose. Rubber withstood the action of the metal rods without splitting. The increased diameter of the tubing within the pump head was necessary in order to obtain the flow rates required in our experiments. The Sigmamotor Company also manufactures a pump with larger pump heads which accommodate larger tubing up to 1 inch in diameter within the pump heads, and thus are capable of accommodating higher flow rates.

Pharmaceal plastic catheters, #12 and #14 French, were used for catheterization of vessels.

Brass connectors, chrome plated, made according to specifications requested, were used in the extracorporeal circuit.

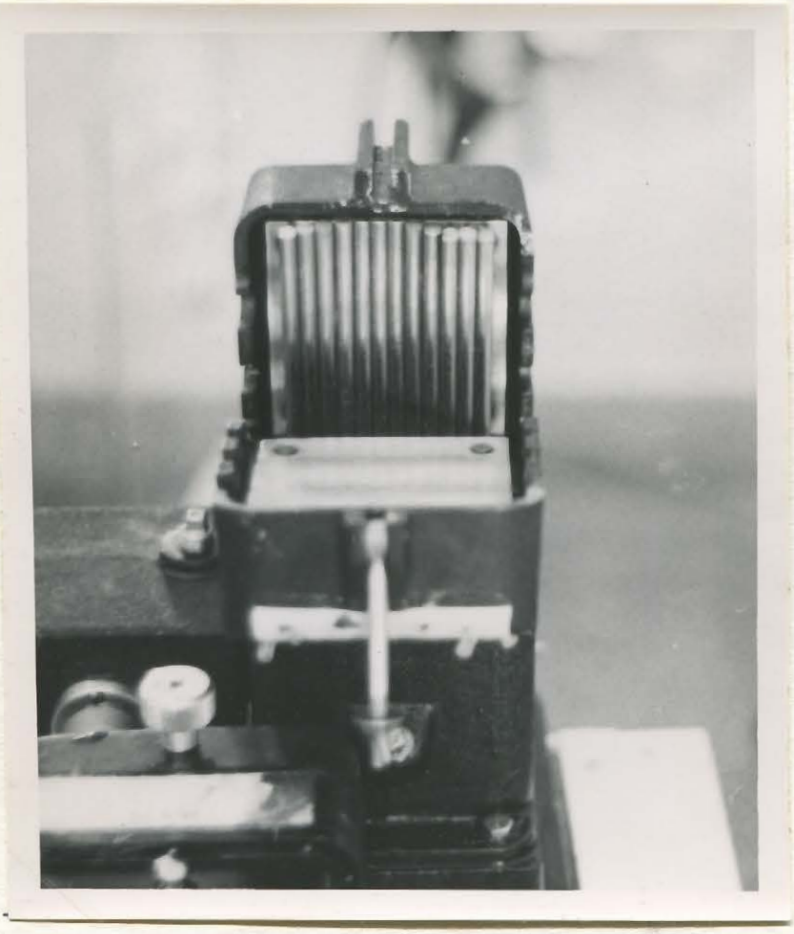

FIGURE 1

Photograph Of a Pump Head Of a Sigmamotor Pump Demonstrating Finger-like Projections.

## Method

Anesthesia:

Both the patient and donor dog were given a general anesthetic for each experiment. Anesthesia was induced by the intravenous injection of sodium pentobarbital in dosage of one grain per 5 pounds body weight. Endotracheal intubation was then carried out in each dog, and each endotracheal tube connected with a mechanical respirator. Positive pressure respiration was maintained throughout the entire experiment. Sodium pentobarbital was given intravenously during the experiment in dosage to maintain the animal in the second stage of anesthesia.

Procedure:

The extracorporeal circuit was sterilized by immersion in 1:1000 zephiran chloride for 24 hours and was assembled using sterile technique.

The circuit was primed with sterile normal saline solution, and the rate of flow of both the arterial and venous pumps was adjusted to deliver 30 c.c. of blood per kilogram body weight of the patient animal per minute.

An intravenous drip was started in one of the superficial veins of the fore-leg of the patient animal. Five per cent glucose in distilled water was administered slowly. This served as a route of administration of intravenous medication during the experiment.

The patient animal was postured in the supine position on an operating table. The neck, chest and the upper portion of the abdomen were shaved and painted with 1:1000 zephiran chloride solution. After appropriate draping for a small incision in the right cervical region and a longer right thoracotomy incision, a small incision was made in the right

cervical region. The right carotid artery and the right jugular vein were exposed and ligated.

The donor animal was postured in the supine position on a second operating table a short distance away from the patient animal. The lower abdomen and groin area was shaved and painted with 1:1000 zepharin chloride solution. After appropriate draping a small vertical incision was made commencing at Poupart's ligament and extending distally over the site of the femoral vessels. The femoral artery and vein were exposed.

A right thoracotomy incision was made in the patient animal. The pleural space was entered by dividing the intercostal muscles in the right fifth interspace. All bleeding points were clamped and ligated. Heavy cotton ligatures were placed about the inferior vena cava at its extrapericardial portion, about the superior vena cava and about the azygos vein. These were left untied at this stage of the experiment.

Heparin in dosage of one mg. heparin per kilogram body weight, was administered intravenously to both the donor and patient animal.

A #14 French catheter was then introduced into the femoral vein of the donor dog and directed cephalad until its tip was judged to lie within the inferior vena cava. A #12 French Pharmaceal catheter was directed cephalad into the femoral artery until its tip was considered to lie within the abdominal aorta.

The ascending aorta of the patient dog was catheterized by way of the previously exposed carotid artery. Finally, a catheter was introduced into the jugular vein and directed caudad until its tip was situated in the inferior vena cava. This last catheter was perforated at its distal

end, and at a more proximal area so that it served to drain blood from both the superior and inferior vena cava.

During insertion of the catheters into the vessels the possibility of air embolization was prevented by filling the catheters with saline prior to insertion.

Before commencing the cross-circulation all connectors were examined, and a careful search for air emboli was made in the "arterial" circuit. Clamps previously placed on all catheters were simultaneously released when the pumps were placed into operation. The ligatures about the superior and inferior venae cavae and the azygos vein were ligated. The mechanical respirator of the patient dog was then stopped and the lungs were maintained in a partially inflated state. During the interval of perfusion the pericardium was incised widely. An incision was made in the right auricle anterior to the insertion of the venae cavae. In one of the three cross-circulation experiments an interauricular septal defect was created and repaired.

Just prior to suturing of the wall of the auricle the ligature about the azygos vein was freed and the auricle allowed to fill with blood. A continuous over and over suture of 000 silk was used to approximate the edges of the incision placed in the wall of the auricle.

The pericardial sac was then loosely closed with widely spaced interrupted silk sutures. This allowed drainage of the pericardial sac and this prevented post-operative cardiac tamponade. The venae caval ligatures were released over a 2 to 4 minute period in order to prevent overdilatation of the heart or the occurrence of cardiac arrhythmia.

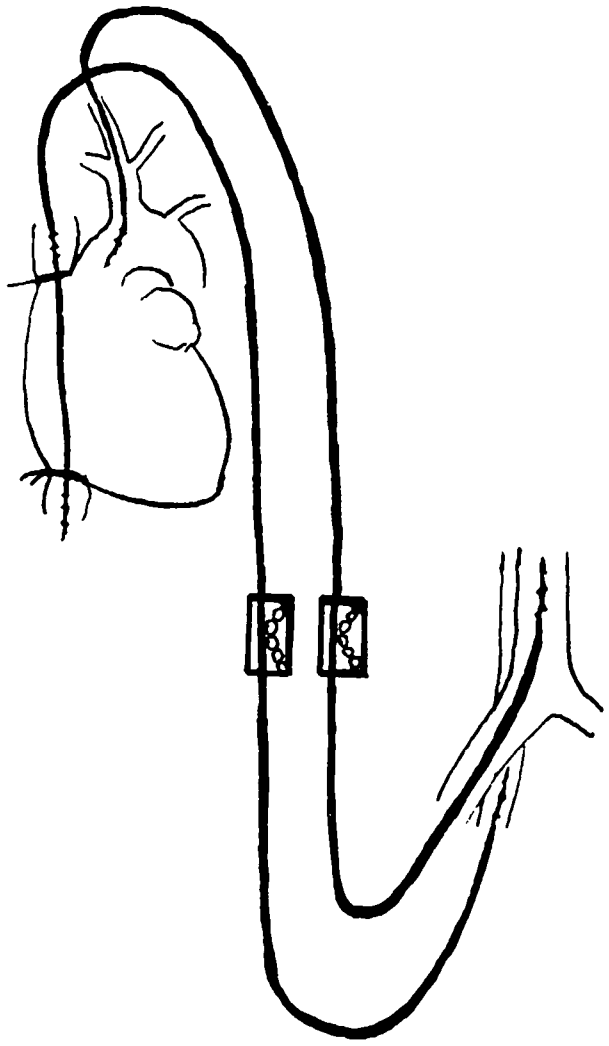

FIGURE 11

Schematic Drawing Demonstrating Catheterization For Cross-Circulation.

The cross-circulation time in the three experiments was 10 minutes, 14 minutes and 18 minutes respectively.

The pumps were stopped immediately after release of the venal caval ligatures and clamps were applied simultaneously to the four plastic catheters which had been introduced into the vessels of the patient and donor dogs.

The lungs of the patient dog were inflated by positive pressure.

The thoracotomy incision was then closed. Pericostal sutures of #5 cotton were used to approximate the ribs. The muscle layers were approximated with interrupted 0 silk sutures. The skin edges were approximated with interrupted mattress #0 cotton sutures. The pleural space was then aspirated of air and fluid.

Results:

All three of the donor animals survived and exhibited no deleterious effects after operation. The patient dog in experiment number one succumbed 4 hours after operation. Autopsy revealed a pneumothorax and 500 c.c. of blood in the pleural space. The patient animals in experiments number 2 and 3 survived. They were normal in every way after operation.

Discussion:

A normal sinus rhythm during exclusion of the heart and lungs of the patient animal from the circulation was noted in all three experiments. The color of the myocardium remained good and the myocardium appeared to be well oxygenated throughout the time of perfusion.

Care was taken in the second and third experiments to inflate the lungs well at the conclusion of the operation and to aspirate the air

and fluid from the pleural space after closure of the chest.

The patient dog in experiment number 3 had a weak and fairly rapid pulse at the conclusion of the operation. He was given an intra-arterial transfusion of 260 c.c. of blood with considerable improvement in his cardiac function. Following this he had a good post-operative course.

Because there existed an element of risk to a donor in any intracardiac procedure carried out with the aid of cross-circulation, this series of experiments was discontinued, and evaluation of biological lung oxygenation was decided upon.

FIGURE 111

Biological Lung Oxygenator.

# CHAPTER IV

## Evaluation of Homologous Lung as an Oxygenator

Materials:

Tygon (180) plastic tubing of internal diameter 3/16 inches (22) was used for the extracorporeal circuit. A double Sigmamotor pump (180) with individually adjustable flow rates was used for propulsion of blood.

Pharmaceal plastic catheters #12 and #14 French were used for insertion into the vessels of the patient animal and into the pulmonary artery of the donor lung. Chrome-plated brass connectors were used in the extracorporeal circuit. Rubber tubing 10/16 inch external diameter was used within the pump heads. The donor lung was suspended in a cylinder made of lucite (Fig. III). This apparatus also served as a collecting chamber and reservoir for oxygenated blood. The reservoir was graduated in 100 c.c. levels for volume determination.

A depulsator (Fig. IV) was used in the circuit just proximal to the inflow line into the pulmonary artery of the donor lung. The depulsator consisted of penrose tubing twisted 180° under tension. It was housed in a plastic container. Metal connectors inserted through rubber stoppers were used to join the depulsator to the Tygon tubing. The rubber stoppers were fitted to the outer plastic chamber housing the penrose drain.

It was reported by Campbell, Crisp and Brown (22) that oedema in the donor lung was considerably reduced when a depulsator was incorporated in the extracorporeal circuit just proximal to the donor lung.

The apparatus was sterilized with zephiran chloride 1:1000 dilution for an 18 hour period (22). The smaller parts were immersed in this solution. The collecting chamber was filled with zepharin.

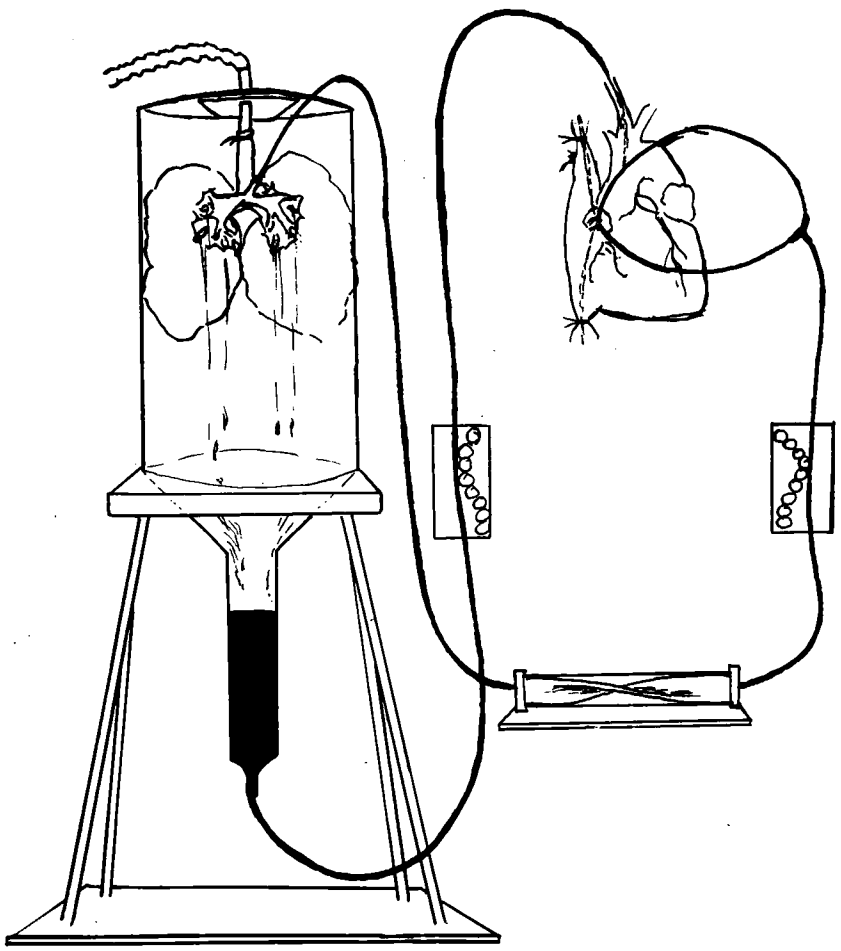

FIGURE 1V

Lung Oxygenator And Extracorporeal Circuit.

The apparatus was assembled under sterile conditions and then rinsed several times with sterile pyrogen-free normal saline by recirculation through the apparatus.

Methods:

Mongrel dogs, weighing approximately 12 kilograms were used for all experiments.

The donor dog was anesthetized by the intravenous injection of sodium pentobarbital. Following this heparin 0.75 mg. per kilogram body weight was administered intravenously. The animal was exsanguinated and the blood collected into sterile vacuum bottles, Baxter Laboratories Incorporated, Morton Grove, Illinois, under sterile technique. The chest was opened and the heart and lungs resected en bloc. The trachea was clamped and divided cephalad to the clamp. The main pulmonary artery was clamped and resected leaving a cuff of conus of the right ventricle attached to it. The pulmonary veins were cut open wide to the lung parenchyma (22), to allow free drainage of blood as it was perfused through the lung. The vascular system of the lungs was then perfused with 500 c.c. of 10 per cent dextran, Glaxo Limited, Toronto, Ontario, 5 per cent glucose solution to which 10 mg. heparin had been added. The dextran was warmed to 37° C prior to perfusion.

A glass connector was placed inside the trachea of the donor lung and secured with heavy cotton suture. This was attached to a mechanical respirator delivering 100 per cent oxygen at 0 to 20 mm. mercury pressure, at a rate of 13, respiratory cycles per minute (Fig. V). The pulmonary artery catheter was placed through a hole in a small rubber stopper which also carried a #12 French catheter for pulmonary artery pressure tracings.

An electromanometer with normal saline in its hydraulic system was employed to record the pulmonary artery pressure. Great care was taken to avoid the entry of air into the pulmonary vascular system during perfusion with dextran and during cannulization of the pulmonary artery. Air emboli in the vascular system of the donor lung appeared to hasten pulmonary oedema.

The patient animal was anaesthetized with sodium pentothal administered intravenously. Electrocardiogram leads were attached to the extremities of the animal for continuous tracing. An endotracheal tube was inserted into the trachea and its proximal end attached to a mechanical intermittent positive pressure respirator.

The animal was postured in the supine position on the operating table. The cervical region, chest and both inguinal regions were shaved and prepared by topical application of zepharin chloride 1:1000 dilution, and then draped.

The patient animal was given heparin intravenously, 0.75 mg. per kilogram body weight.

A small incision was then made in the inguinal region and the femoral artery was exposed. A small plastic catheter was inserted into the femoral artery and advanced until its tip lay in the aorta. This was connected to a manometer and kymograph system for continuous arterial pressure recording.

A small transverse incision approximately 3 cm. in length was made in the right supraclavicular region. The right external carotid artery and jugular vein were exposed. The carotid artery was catheterized with a number 14 French plastic catheter and advanced so that its terminal

perforations lay just within the ascending aorta. Its distal end was temporarily stoppered with a rubber stopper. The jugular vein was catheterized with a number 12 French catheter. This was advanced so that its tip lay in the inferior vena cava just superior to the level of the diaphragm. This catheter contained two sets of perforations, one at its distal end and a second set at its mid-portion. This allowed simultaneous drainage of both the superior and inferior venae cavae. This catheter was also temporarily stoppered with a rubber stopper.

A right thoracotomy was performed, the pleural space entered through the fifth interspace and the ribs retracted by means of a Finnochietti retractor. Heavy cotton ligatures were placed about the azygos vein, the superior vena cava and the inferior vena cava. The extracorporeal circuit was primed with heparinized donor blood. The arterial and venous catheters previously inserted in the patient animal were connected to the appropriate arterial and venous lines of the extracorporeal circuit.

The ligatures about the azygos vein, the superior vena cava and the inferior vena cava were ligated and the pump started. The mechanical respirator was disconnected from the patient animal.

The pericardium of the patient animal was excised down to the base of the heart and along the right lateral border. In three experiments an incision was made in the wall of the right auricle anterior to the insertion of the venae cavae. An inter-atrial septal defect was created and repaired in two experiments. The coronary venous blood was aspirated intermittently, but this blood was not returned to the extracorporeal circuit. In 21 experiments an incision was made in the wall of

the right ventricle. This was placed parallel with the anterior descending branch of the left coronary artery.

A pulmonary artery pressure tracing of the donor lung was taken during perfusion of the patient animal. Results are recorded in Table II and Figure XII. Rectal temperature readings were made during the experiment and any fall in temperature during perfusion was recorded.

The arterial and venous pumps were monitered constantly during perfusion in order to maintain an inflow and outflow balance. The heart was constantly observed during perfusion, attention being given to the color of the myocardium, the cardiac rate and rhythm. The myocardium was sutured with continuous 000 silk suture. Just prior to placing the last stitch the ligature on the azygos vein was released and the heart allowed to fill with blood.

Immediately upon cessation of perfusion the mechanical respirator was connected to the endotracheal tube and the lungs were inflated with intermittent positive pressure both manual and mechanical. The mechanical respirator was then used until the conclusion of the operation.

The ligatures about the superior and inferior venae cavae were released gradually over a two to three minute period. The superior vena cava was released first and the heart was observed for evidence of arrhythmia or distension. The inferior vena caval ligature was then released gradually.

The chest incision was then closed. Heavy cotton pericostal sutures were first placed to approximate the ribs. The muscle layers were approximated with continuous cotton suture. The skin edges were approximated with interrupted mattress sutures of cotton #0.

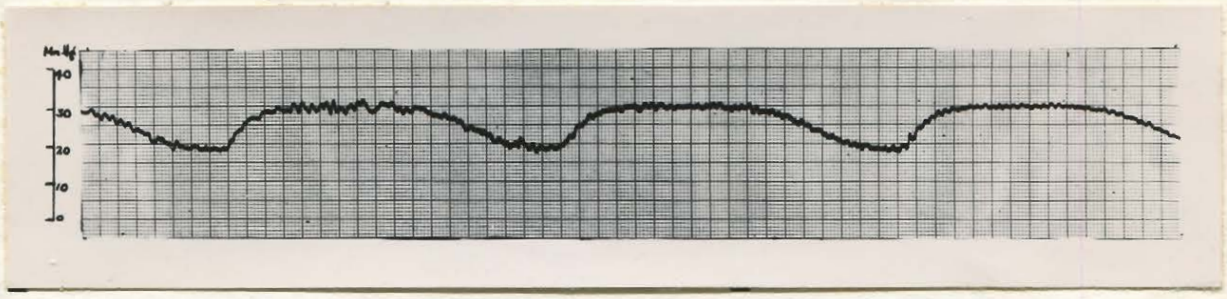


FIGURE V

Endotracheal Pressure In Homologous Lung Oxygenator.

The lungs were well inflated and the chest cavity was aspirated of air and any blood that was present.

Protamine sulfate 50 mg. of one per cent solution was given intravenously to the patient animal.

Biopsies of the donor lung were taken for microscopic examination.

In experiments in which only one lobe of lung tissue was used as an oxygenator the procedure for resection of the donor lung was simplified. The same precautions were taken to avoid the introduction of air emboli into the vascular system of the lobe as when the entire lungs were used as an oxygenator.

One of the complications that arose in our experiments was oedema of the donor lung during perfusion. Because of this, in experiment XI, an attempt was made to evaluate the effect of perfusion substances in artificially respired dog's lungs. The perfusion substances tested were:

1. Dextran 10 per cent with glucose 5 per cent.
2. Plasma.
3. Autogenous heparinized whole blood.
4. Normal saline.

For the lobes through which plasma and whole blood were perfused a negative pressure respiratory apparatus was constructed. This consisted of a vacuum container in which an intermittent negative pressure of 0 to 9 mm. mercury was produced.

For the lobes through which dextran and saline were perfused an intermittent positive pressure respiratory mechanism delivering 100 per cent oxygen at 0 to 14 mm. mercury pressure was used.

The donor lobes were weighed prior to perfusion, and again after perfusion. This is recorded in Table III. Sections of the donor lobes were taken for microscopic examination just after perfusion.

The large polysaccharide molecule of dextran did not cross the alveolar barrier and thus pulmonary oedema did not occur with dextran perfusion, but some septal oedema was noted on section, Fig. VI, VII.

Normal saline readily crossed the alveolar septum and pulmonary oedema occurred in the donor lobe after 3 minutes perfusion of normal saline, Fig. IX.

Plasma and whole blood remained entirely within the vascular tree of the donor lung and none was seen in the alveoli on section of the lobes which had been perfused with plasma and whole blood, Fig. VIII, X.

FIGURE VI

Microphotograph

Magnification X 400 Perfusion Of Lung With Dextran 10%

Glucose 5% Inter-septal Edema.

FIGURE V11

Microphotograph

Magnification X 400 Perfusion of Lung With Dextran 10%

Glucose 5% Normal Lung.

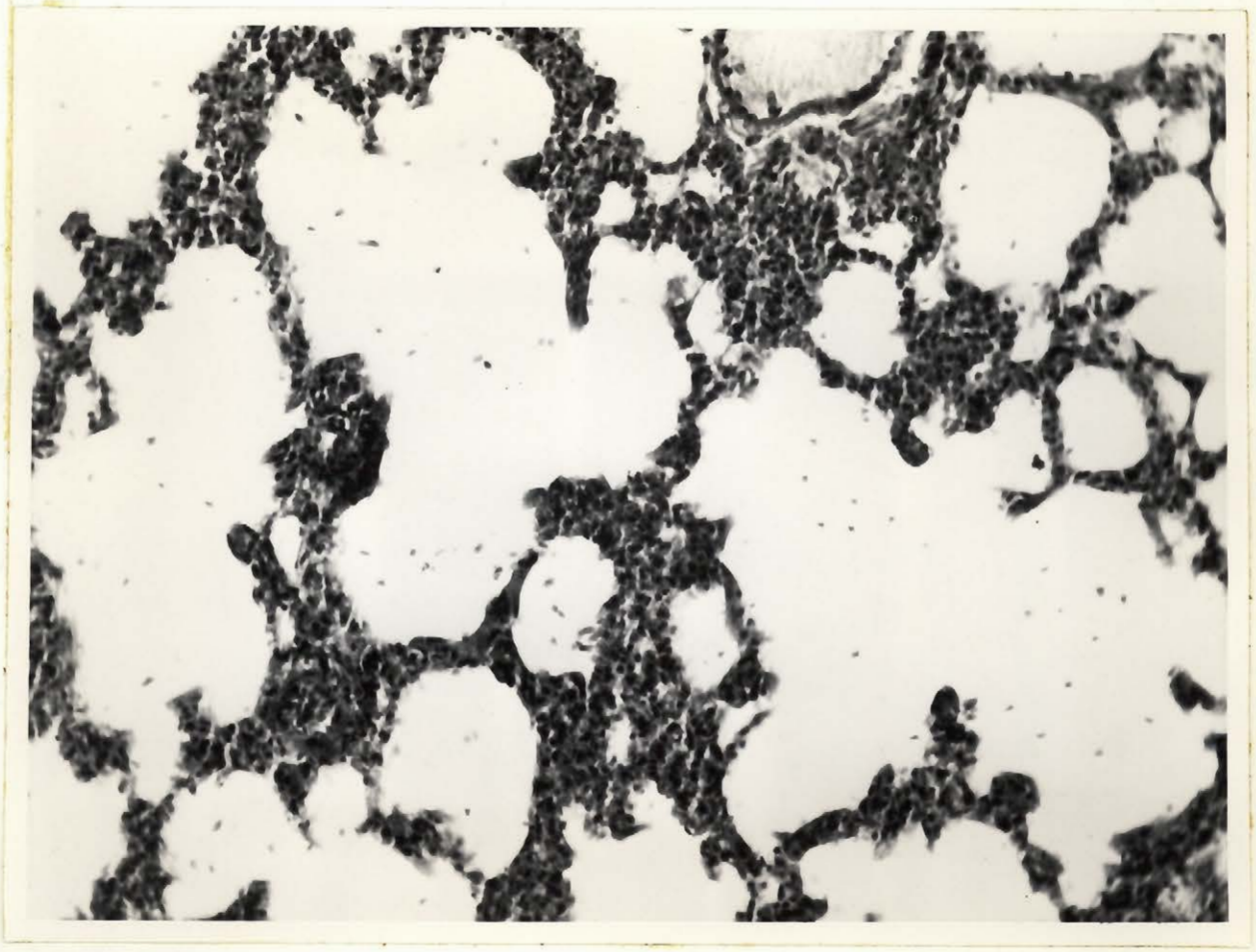

FIGURE VIII

Microphotograph

Magnification X 400 Perfusion of Dog Lung With Human Plasma

Normal Lung.

FIGURE 1X

Microphotograph

Magnification X 400 Perfusion of Lung With Normal Saline

Alveolar Edema.

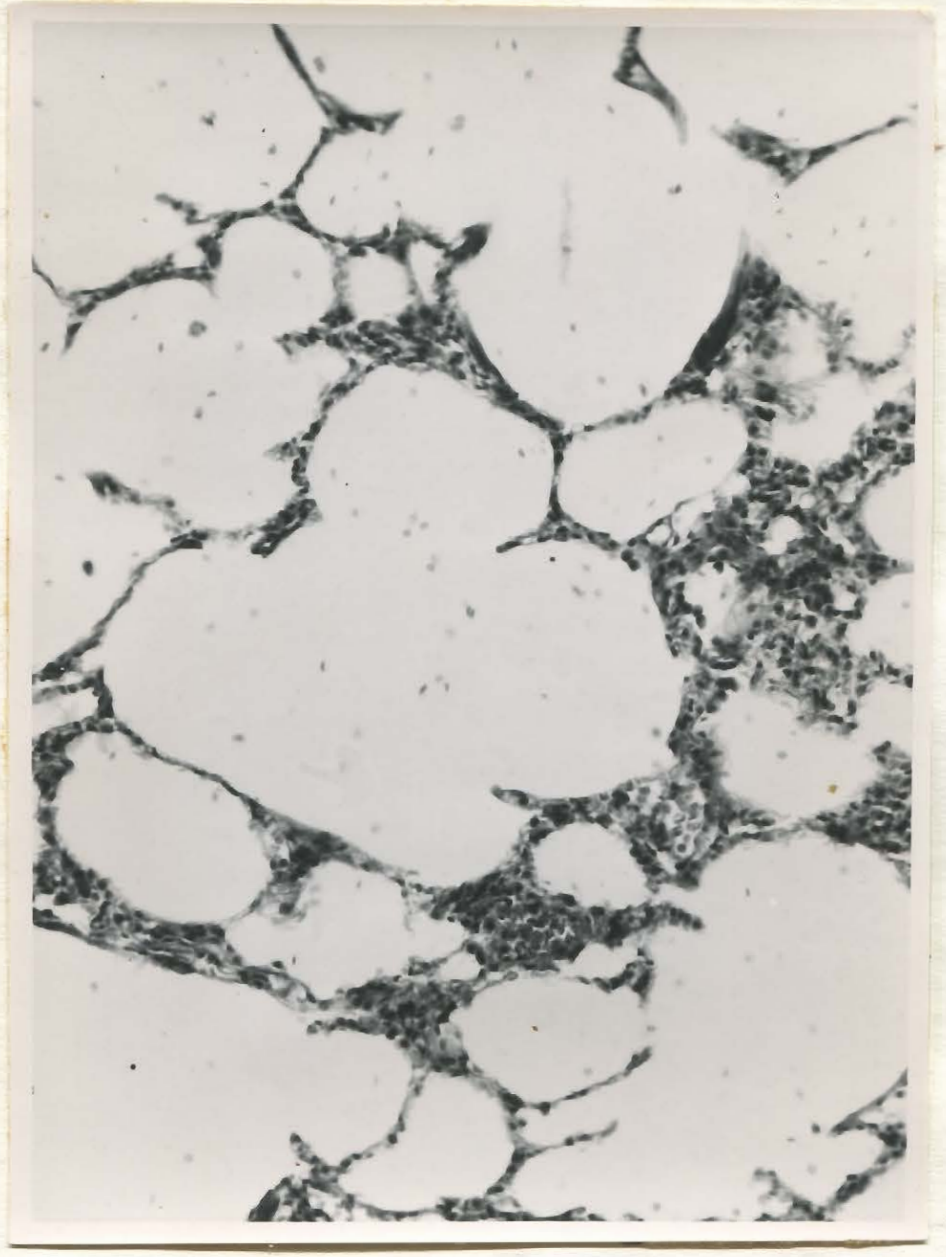

FIGURE X

Microphotograph

Magnification X 400 Perfusion of Lung With Autogenous Blood-Normal Lung.

TABLE 11

FUNCTION OF DONOR LUNG

| Tissue | Exp. No. | Endotrocheal Pressure Mm. Hg. | Perf-usion Rate cc/min. | Perf-usion Press. Mm. Hg. | Dir-ection of Fun-ction Min. | Final Gross Appearance | Wt. Gain Gm. | Perfusion Substance |
|---|---|---|---|---|---|---|---|---|
| Lung | 6 | | 354 | | 20 | Normal | | 1. Dextran<br>2. Blood |
| Lung | 7 | | 435 | | 10 | Edema Lower Lobe | | 1. Normal Saline<br>2. Blood |
| Lung | 8 | 0 to 11 | 504 | | 26 | Insufficient Oxygenation | | 1. Dextran<br>2. Glucose<br>3. Blood |
| Lung | 9 | | 520 | | 25 | Normal | | 1. Dextran<br>2. Glucose<br>3. Blood |
| Lung | 10 | | 600 | | 9 | Air Emboli Lung Hemorrhagic. Arterio-Venous Shunt | | 1. Glucose<br>2. Blood |
| Lobe | 11 | 0 to 14 | 350 | | 40 | Edema Post. Segment | 103 | Dextran |
| Lobe | 11 | 0 to -3 | 350 | | 26 | Edema, Dependant | 316 | Plasma |
| Lobe | 11 | 0 to 14 | 350 | | 3 | Edema, Generalized | 102 | Normal Saline |
| Lobe | 11 | 0 to -2 | 350 | | 27 | Edema, Dependant | 331 | Blood |
| Lobe | 12 | 0 to -17 | 350 | | 35 | Edema, Dependant | 61 | Blood |
| Lobe | 12 | 0 to 15 | 350 | | 5 | Fluid in Bronchus Edema | 50 | Dextran |

TABLE 11. Continued

| Tissue | Exp. No. | Endotrocheal Pressure Mm. Hg. | Perf-usion Rate cc/min. | Perf-usion Press. Mm. Hg. | Dir-ection of Fun-ction Min. | Final Gross Appearance | Wt. Gain Gm. | Perfusion Substance |
|---|---|---|---|---|---|---|---|---|
| Lobe | 13 | Neg. | 435 | | | Some Edema | | Blood |
| Lobe | 14 | Pos. | 465 | | 11 | Normal | | 1. Dextran<br>2. Blood |
| Lobe | 15 | Pos. | 400 | | 12 | Shunt Edema | 50 | 1. Dextran<br>2. Blood |
| Lung | 20 | 0 to 16 | 440 | 4-10 | 19 | Normal | | Dextran |
| Lung | 20 | 0 to 16 | 440 | 10-26 | 42 | Normal | | Blood |
| Lung | 21 | 0 to 40 | 200 | 6-29 | 45 | Normal | | 1. Dextran<br>2. Blood |
| Lung | 22 | 0 to 20 | 480 | 13-18 | 32 | Slight Edema | | 1. Dextran<br>2. Blood |
| Lung | 23 | 0 to 28 | 408 | 20-24 | 30 | Normal | 70 | 1. Dextran<br>2. Blood |
| Lung | 24 | 0 to 20 | 330 | 10 | 31 | Normal | | 1. Dextran<br>2. Blood |
| Lung | 25 | 0 to 20 | 420 | 15-20 | 30 | Normal | 82 | Blood |
| Lung | 27 | 0 to 20 | 546 | 13-16 | 30 | Normal | 55 | 1. Dextran<br>2. Blood |
| Lung | 28 | 0 to 22 | 520 | | 16 | Normal | 55 | 1. Dextran<br>2. Blood |

TABLE 11, Continued

| Tissue | Exp. No. | Endotrocheal Pressure Mm. Hg. | Perf-usion Rate cc/min. | Perf-usion Press. Mm. Hg. | Dir-ection of Fun-ction Min. | Final Gross Appearance | Wt. Gain Gm. | Perfusion Substance |
|---|---|---|---|---|---|---|---|---|
| Lung | 29 | 0 to 20 | 510 | 20-40 | 30 | Normal | 35 | 1. Dextran<br>2. Blood |
| Lung | 30 | 0 to 20 | 460 | 3-5 | 30 | Normal | 65 | 1. Dextran<br>2. Blood |
| Lung | 31 | 0 to 20 | 500 | | 30 | Normal | | 1. Dextran<br>2. Blood |
| Lung | 32 | 0 to 18 | 400 | | | Normal | | 1. Dextran<br>2. Blood |
| Lung | 33 | 0 to 22 | 420 | 22 | 20 | Normal | 20 | 1. Dextran<br>2. Blood |
| Lung | 34 | Pos. | 525 | | 30 | Normal | | 1. Dextran<br>2. Blood |

TABLE 111

EFFECTS OF PERFUSION SUBSTANCES ON DONOR LUNG

Sept. 16/55

Experiment X1

| DATA: | 1. | 2. | 3. | 4. |
|---|---|---|---|---|
| 1. Perfusion Fluid | Dextran 10% Gluc. 5% | Plasma | Normal Saline | Heparinized Blood |
| 2. Substance respirated | 100% Ox. | Air | 100% Ox. | Air |
| 3. Respirator pressure system | pos. | neg. | pos. | neg. |
| 4. Respiratory excursion | 0 to 14 mgm. Hg. | 0 to 3 mm. Hg. (Ave.) | 0 to 14 (Ave.) | 0 to 2 (Ave.) |
| 5. Resp. rate | 19/min. | ? | 19/min. | ? |
| 6. Time respirator started | 11.35 | 12.10 | 1.14 | 1.29 |
| 7. Time Flow started | 11.40 | 12.14 | 1.15 | 1.37 |
| 8. Time Flow stopped | 12.20 | 12.40 | 1.25 | 2.04 |
| 9. Perfusion time | 40 mins. | 26 mins. | 10 mins. | 27 mins. |
| 10. Initial wt. | 50 gm. | 44 gm. | 28 gm. | 35 gm. |
| 11. Final wt. | 153 gm. | 360 gm. | 130 gm. | 366 gm. |
| 12. Wt. increased | 103 gm. | 316 gm. | 102 gm. | 331 gm. |
| 13. Time Oedema first noted | 11.45 post seg. | 12.33 dependent | 1.18 entire | 1.43 dependent |
| 14. Time of total oedema & non-function | - | 12.40 | 1.18 | 2.04 |

TABLE 111, Continued

| DATA: | 1. | 2. | 3. | 4. |
|---|---|---|---|---|
| 15. Duration of Function | 40 mins. | 26 mins. | 3 mins. | 27 mins. |
| 16. Path. specimen no. | 1,2, | 3 | 4 | 5 |
| 17. Addition of perfusion fluid | None | 20cc | None | 50cc<br>50cc<br>25cc |

Path. Specimens (1) - Septal oedema

(2) - Normal

(3) - Normal

(4) - Alveolar oedema

(5) - Normal

Results and Discussion:

Of the group of 26 operations utilizing extracorporeal circulation and homologous lung oxygenation there were five long term survivals as listed in Table XI.

In three experiments, numbers XIII, XIV and XV, a lobe of the lung was used as an oxygenator. There were no long term survivors in this group. Anoxia would appear to be a factor.

In experiment XIII, Table I, the donor lobe was inverted to facilitate drainage of any endobronchial secretions that might accumulate in the bronchial tree. Intermittent negative pressure breathing was used. At the conclusion of perfusion ventricular fibrillation occurred. Air emboli had been inadvertently introduced into the extracorporeal circuit and coronary air emboli were observed in the heart. The heart did not regain function.

In experiment XIV the donor lobe was suspended in a container and connected to a positive pressure respirator apparatus. Perfusion time in this experiment was 19 minutes. The right ventricle was open for 3 minutes. Ventricular fibrillation occurred after 19 minutes perfusion, 13 minutes after the ventricular incision was sutured. Intra-arterial transfusion, calcium chloride, adrenalin chloride and defibrillation and cardiac massage were all administered, but the heart did not regain function.

In experiment XV the lobe was suspended and connected to a positive pressure mechanical respirator. Perfusion time was 12 minutes. The right ventricle was open for 5 minutes. The heart maintained a good color and a regular rhythm throughout the entire procedure. The animal succumbed

48 hours post-operatively. At autopsy 400 c.c. of blood was found in the chest cavity. The animal apparently died of post-operative blood loss.

In the twenty-three experiments in which the entire lungs were used as homologous oxygenators there were five long term survivors. The blood flow rate in all of these experiments was 30 c.c. per kilogram per pound body weight of patient animal per minute. The perfusion time and exclusion of the heart and lungs of the patient animal ranged between 8.5 and 31 minutes. The heart was open for an interval from 2.5 to 13 minutes. The arterial blood pressure fell abruptly from 90 to 120 mm. mercury pressure to 30 to 40 mm. mercury pressure upon exclusion of the heart and lungs from the circulation. The pressure ranged between 20 and 50 mm. mercury pressure during perfusion and gradually rose to initial levels, or even slightly higher in some experiments after release of the venae cavae and resumption of corporeal circulation, Fig. XI, XIV, XVI.

The causes of death are listed in Table XI. Post-operative blood loss was revealed at autopsy in four cases. In ten experiments the brachio-cephalic artery was divided in error. There was one death for each of the following causes: air emboli in the extracorporeal system, ventricular fibrillation during perfusion, empyema and septicemia, distemper and pneumonia. The first two of these deaths were operative, and the last two occurred in the post-operative period.

The five animals which survived operation had uneventful operative and post-operative courses. In these experiments the myocardium maintained a good color during perfusion and the heart maintained a regular sinus rhythm, Fig. XIII, XV. The heart took over function after perfusion

with no evidence of arrhythmia or distension. The animals survived for periods from 2 months to 6 months post-operative until they were sacrificed for further experimental work. The animals appeared entirely normal in every way post-operatively. At autopsy the myocardial incision in each case was well healed and the heart appeared normal in every way.

Laboratory determinations as blood oxygen saturation, Table V, blood carbon dioxide content, Table VII, blood pH values, Table VIII, will be discussed in the general evaluation of all our experiments with extra-corporeal circulation.

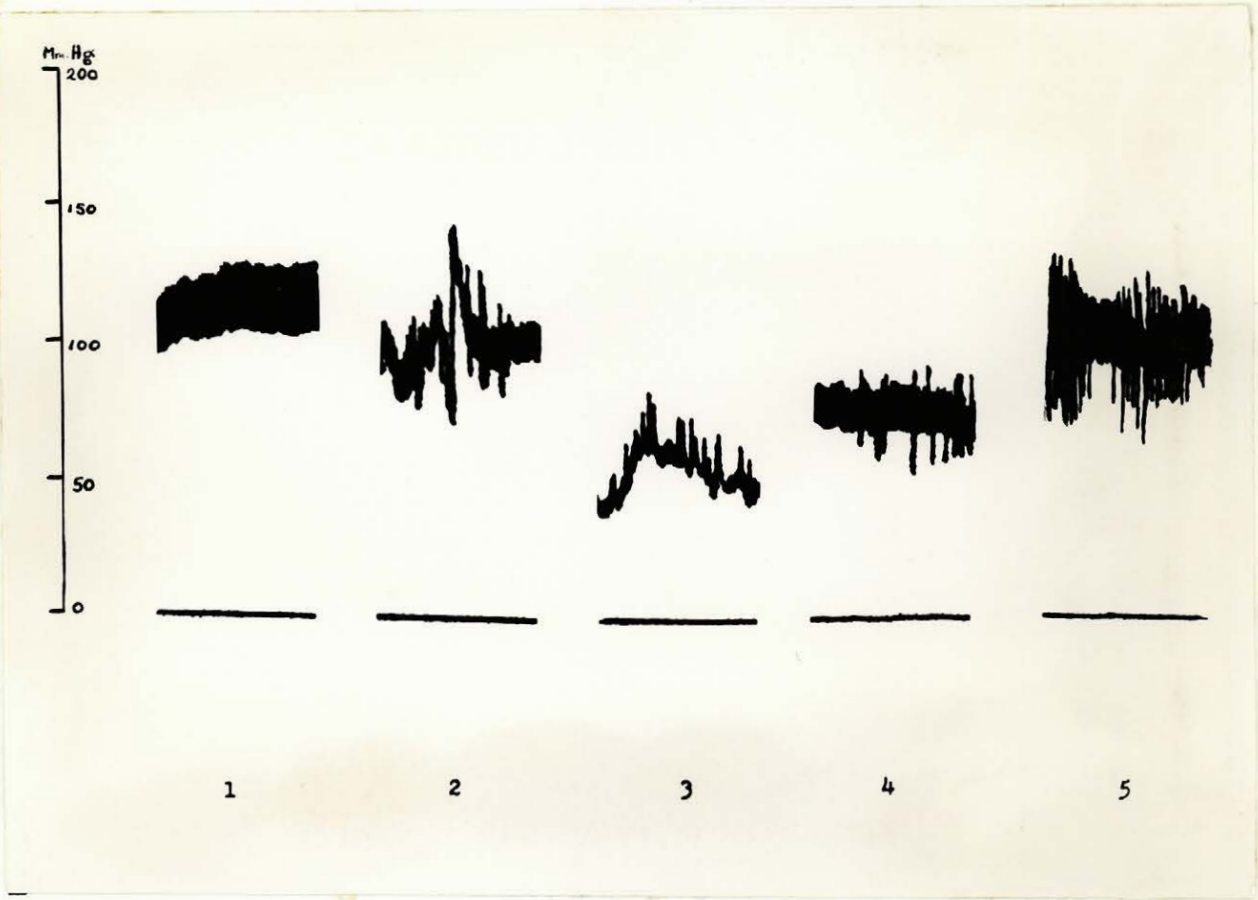


FIGURE XI

Arterial Pressure Tracing Homologous Lung Oxygenation Cardiotomy, Right Ventricle.

Experiment 37.

1. Initial blood pressure
2. Chest open
3. Occlusion of venae cavae and biological oxygenation
4. Corporeal circulation re-instituted
5. Chest closed

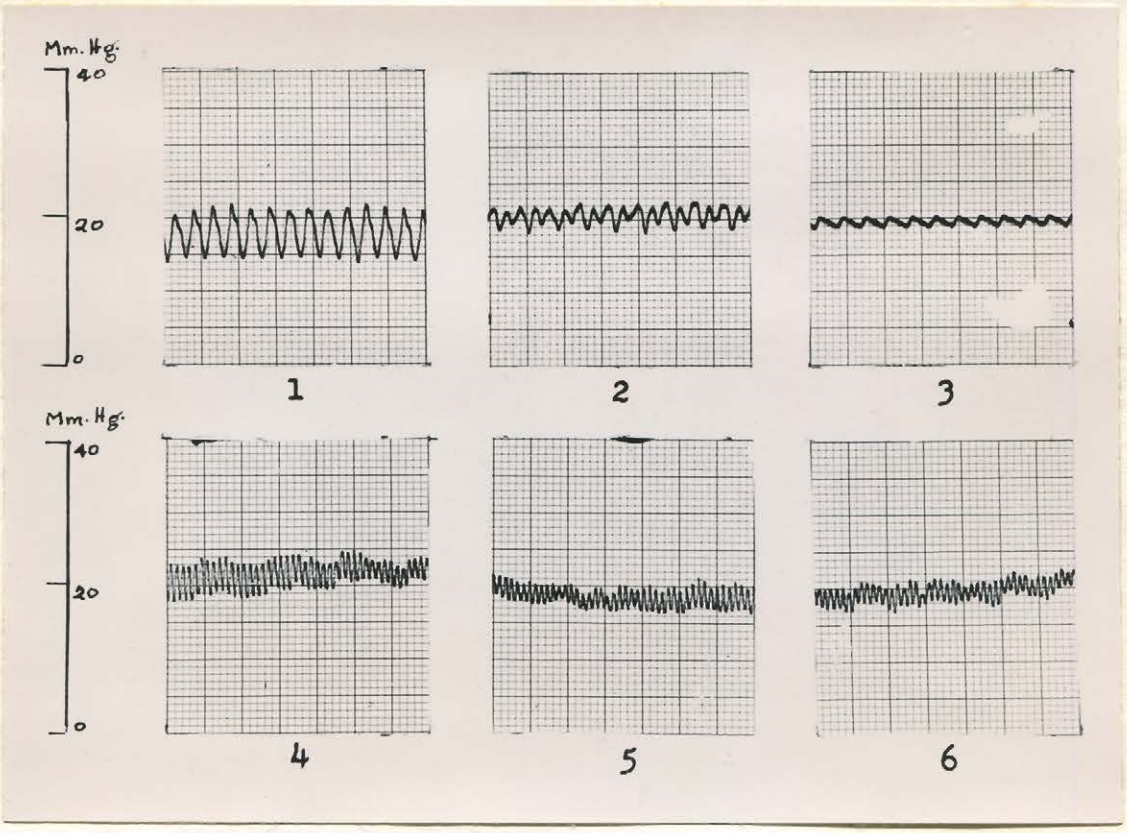


FIGURE XII

Pulmonary Artery Pressure In Lung Oxygenator.

Experiment 21.

1. Perfusion

2. Perfusion

3. Perfusion - cardiotomy right auricle.

Experiment 25.

4. Perfusion

5. Perfusion

6. Perfusion.

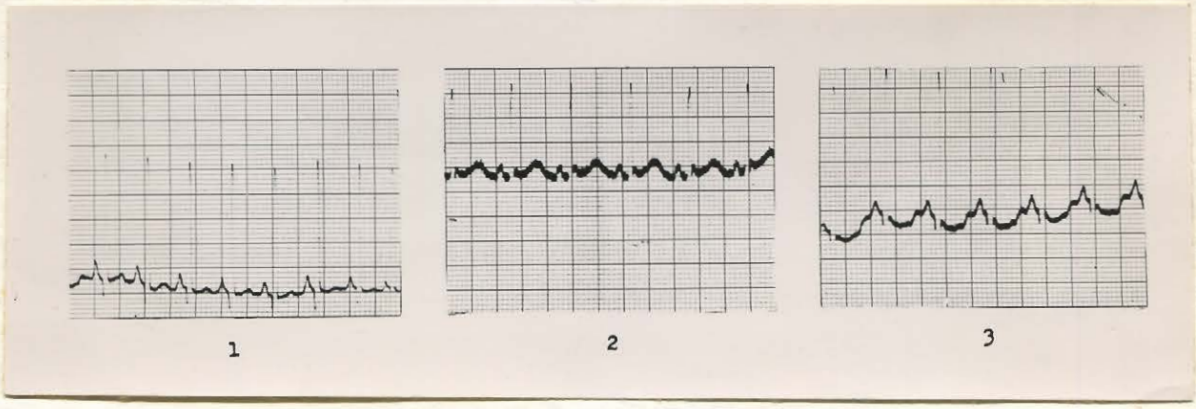


FIGURE XIII

Electrocardiogram.

Homologous Lung Oxygenation.Cardiotomy, Right Ventricle.

Experiment 40.

1. Chest open

2. Occlusion of Venae Cavae

3. Chest closed.

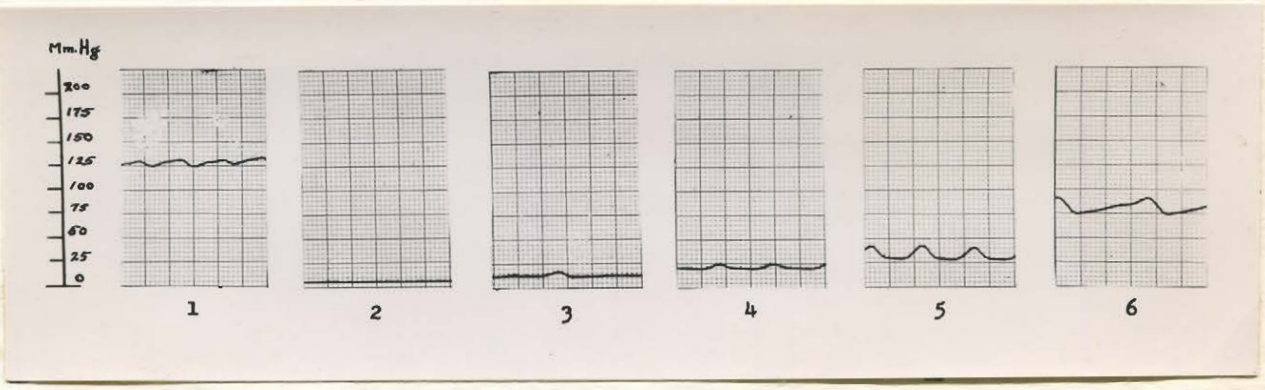


FIGURE XLV

Femoral Artery Pressure Tracing Homologous Lung Oxygenation

Cardiotomy, Right Ventricle.

Experiment 33.

1. Chest open
2. Perfusion - ventricular fibrillation
3. Perfusion - sinus rhythm
4. Perfusion - sinus rhythm
5. Corporeal circulation re-instituted
6. Chest closed.

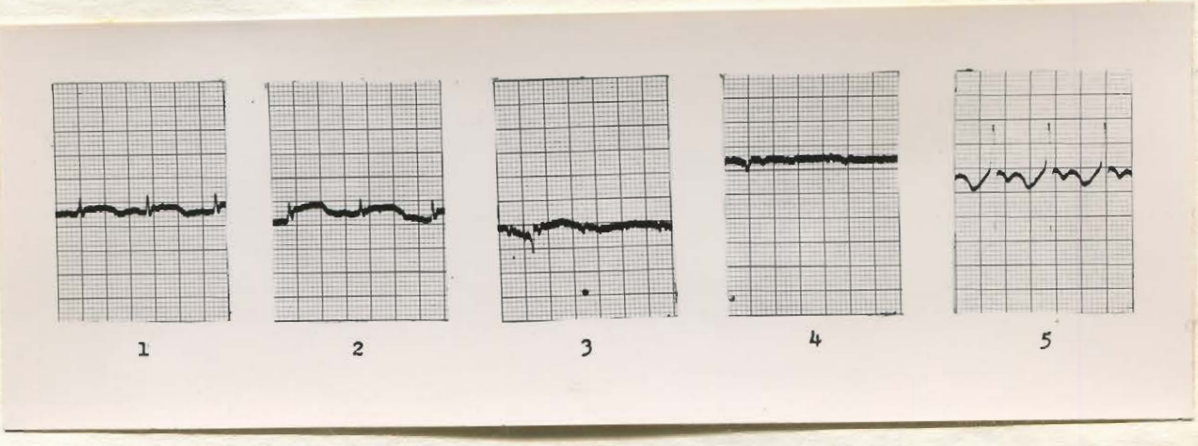


FIGURE XV

Electrocardiogram Lead $\overline{111}$

Homologous Lung Oxygenation.Cardiotomy, Right Ventricle.

Experiment 39.

1. Chest open
2. Perfusion
3. Release of ligatures about venae cavae
4. Corporeal circulation 10 minutes later
5. Chest closed.

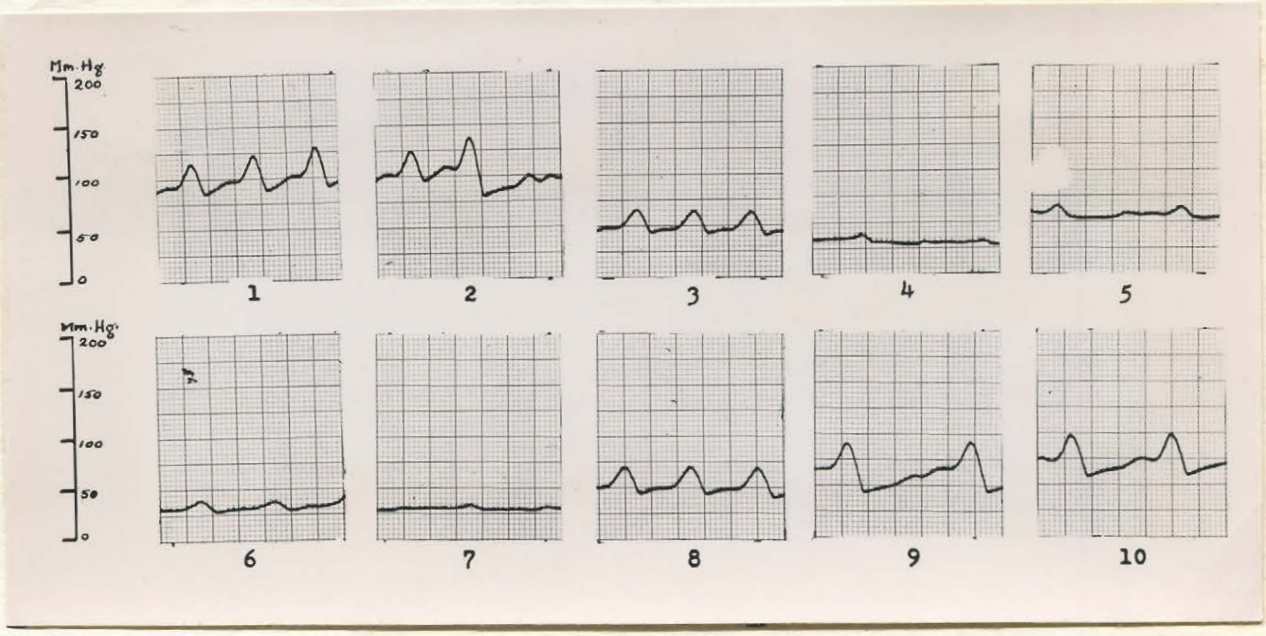


FIGURE XVI

Arterial Blood Pressure Recorded In Abdominal Aorta Homologous Lung Oxygenation.Cardiotomy, Right Ventricle.

Experiment 31.

1. Initial
2. Purse string placed in right auricle
3. SVC and IVC cannulated
4. Perfusion
5. Perfusion
6. SVC released
7. SVC and IVC open
8. Blood 150 cc intra-arterial
9. Blood 100 cc intra-arterial
10. Venous catheters removed.

## CHAPTER V

### Evaluation of Artificial Oxygenation and Extracorporeal Circulation

Introduction:

Inspired by the success of the group at the University of Minnesota, in the field of open cardiac surgery, with the aid of the Lillehei - De Wall type of artificial oxygenator (131), we elected to experiment with artificial oxygenation on the principle of bubbling oxygen through blood.

Clark, Gollan and Gupta (27) were able to obtain very rapid and efficient oxygenation of blood by foaming it in an artificial oxygenator by gas dispersion. A defoaming agent, a silicone substance known as DC Antifoam A, Dow Corning Corporation, Midland, Michigan. This was a methylsiloxane resin which was used industrially as a defoaming agent, and was considered non-toxic in vivo.

The bubbler type of oxygenator, as used by Lillehei et al, incorporated the basic principles of the Clark oxygenator. However, whereas the oxygenator of Clark, Gollan and Gupta was constructed mainly of glass and rubber tubing, the Lillehei - De Wall oxygenator was constructed almost entirely of plastic substances. This was considered ideal for an extracorporeal system, as the clotting tendency of blood in contact with plastic was very low. The loss of platelets and other blood elements was also low.

Goertner and Briggs (73) in 1928 postulated that the initial step in blood clotting involved a surface concentration of some positively charged constituent, the concentration being brought about by selective adsorption. Substances which decrease surface or interfacial tension tend to be adsorbed. Possibly blood clotting is dependent upon the adsorption of some constituent of the serum onto a surface, thereby increasing the

effective concentration of the constituent and thereby increasing the clotting phenomenon.

By streaming potential measurement a bare glass capillary had a negative streaming potential of approximately 30 mv. When the same glass capillary was coated with a thin layer of paraffin it had essentially a zero potential against water.

A high streaming potential would favor electrostatic adsorption of positively charged colloids at the interface of glass-blood serum, and there would be no such tendency for paraffin-blood serum.

Hirschboeck, in 1941 (84), observed that blood coagulation time in methyl methacrylate tubes was found to be twice as long as the coagulation time in glass tubes.

Ingraham et al. (92), in 1947 reported on a new synthetic plastic, polyethylene, for use in surgery. It was described as a long chain polymer of ethylene first produced in 1936 in Great Britain by the process of polymerization of ethylene under extremely high pressures. The final result was a micro crystalline, slightly cloudy, thromboplastic resin with electrical insulating properties.

Rowe et al. (174) 1948 in experiments with laboratory animals showed that the silicones, methyl and mixed methylphenyl polysiloxanes as a class are very low in toxicity.

Donovan (44) stated that polyethylenes chemical structure, clot retraction and repelling action on water were similar to paraffin and therefore it probably delayed coagulability in a similar way, that is, by its relative inertness to the clotting colloids of blood and through its protective action on the stability of platelets.

Glassman, (70) in 1950, showed that there existed a correlation between the cytolytic power, surface activity and electrostatic interaction of anionic surface-active agents and the lipid, lipoprotein and protein compounds of the red blood cell ultrastructure. The author studied two nonionic compounds Tritons WR 135 and A20. Both were non-hemolytic and non-toxic.

Rednight (172) in 1954 reported that the solubility of oxygen in silicone fluids was surprisingly high.

The high solubility of oxygen in silicone substances is probably the mechanism of action of DC antifoam A as a defoaming agent.

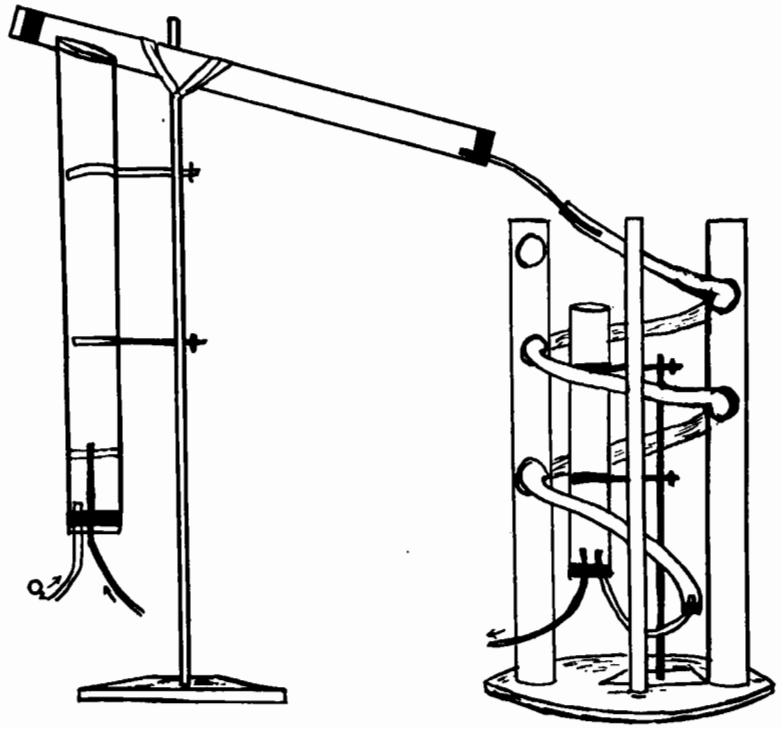

FIGURE XVll

Artificial Oxygenator

Apparatus 1.

## Artificial Oxygenation Experiments

Materials:

Four modifications of a simple oxygenator apparatus were used in our experiments.

Apparatus I.

Mayon (140) plastic tubing, 2 inches internal diameter was used for the oxygenating chamber. It was held in a vertical position by clamps attached to a metal stand. The lower end of this tubing was stoppered with a rubber stopper through which we had inserted a small glass cannula for oxygen inflow and Tygon tubing for blood inflow. The Tygon tubing extended upward through a hole placed centrally in a nylon plate made to fit snugly to the inner surface of the Mayon tubing. The rest of the plate was multi-perforated with holes 1/64 inch in diameter which permitted the entry of oxygen upward, but, when the pump was in motion, prevented blood from dripping through the plate. The nylon plate was 1/4 inch in thickness.

The defoaming chamber was Mayon plastic tubing of 1 1/2 inch internal diameter set at an angle to the horizontal plane and connected with the top of the bubbling chamber. The upper end was stoppered with a rubber stopper which had a perforation 1/4 inch in diameter at its upper portion. The lower end was stoppered with a rubber stopper which held a fairly short length of Tygon plastic tubing. The lumen of the defoaming chamber was lined with anafoam, DC antifoam A (46).

The collecting chamber was a helix which consisted of Mayon plastic tubing of 1 inch internal diameter. It was supported by a wooden frame with two inch holes placed at appropriate levels, Fig. XVII.

The upper portion of the helix was left open and the lower end of the short length of Tygon tubing leading from the defoaming chamber was loosely placed with its tip about 8 inches below the upper opening of the helix. The lower end was stoppered with a rubber stopper which held a length of Tygon tubing. The inner surface of the lower portion of the helix was coated with anafoam.

The reservoir consisting of a length of Mayon plastic tubing 1 1/2 inch internal diameter was constructed. Its upper end was open. Its lower end was stoppered with a rubber stopper which held one end of the Tygon tubing connected to the helix, and one end of the Tygon tubing which led to the arterial pump.

Rubber tubing of 1/2 inch internal diameter was placed within the head of the Sigmamotor pump. The remainder of the arterial line was Tygon tubing. A similar venous line consisted of Tygon tubing, and the tubing within the venous pump head was identical with the tubing in the arterial pump head.

The jugular vein was catheterized with a plastic catheter size #12 or #14 French. This catheter was perforated at its tip and had a second set of perforations at its mid-level to allow for simultaneous drainage of the inferior and superior vena cava. The tip was advanced into the inferior vena cava.

The arterial catheter was also plastic #12 or #14 French but had only one set of perforations at its tip. The catheter was advanced by way of the carotid artery to the ascending aorta.

Apparatus II.

This modification was fashioned after the method of Lillehei (131).

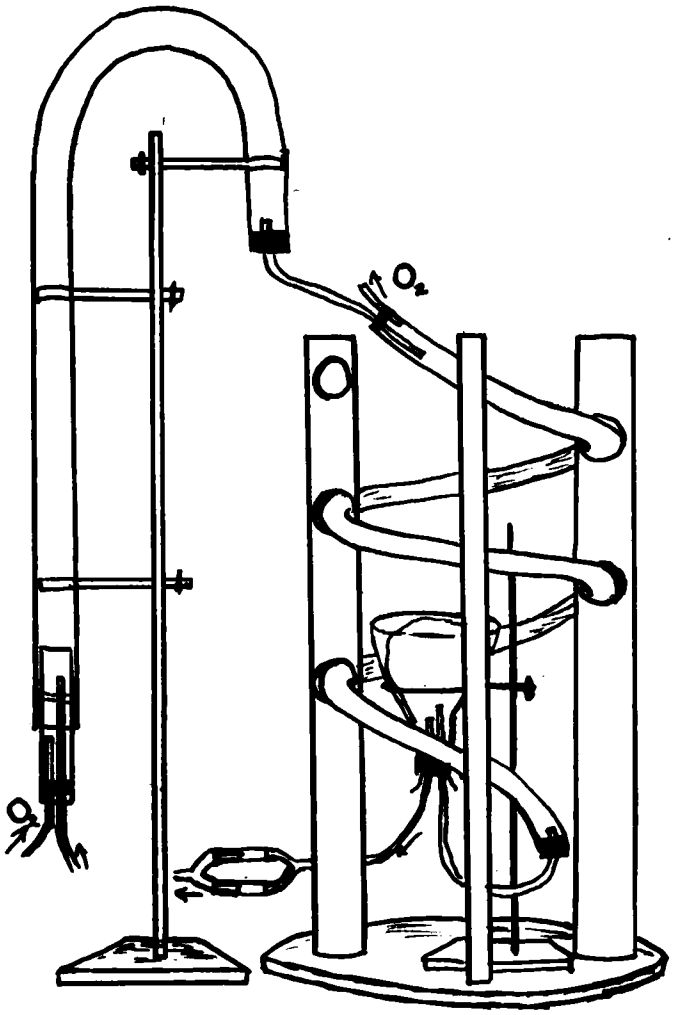


FIGURE XVlll

Artificial Oxygenator

Apparatus 2.

The bubbling and defoaming chambers were combined in one length of Mayon tubing 1 1/2 inch internal diameter, the upper portion of which was turned in an inverted V shape as in Fig. XVIII.

An oxygenator unit made of lucite and containing a perforated nylon plate was placed in the lower portion of the tubing. A rubber stopper at its lower end held a small glass rod for oxygen inlet and a lower lucite rod which extended through the perforated nylon plate for inlet of venous blood.

The upper end of the Mayon tubing was stoppered with a rubber stopper which held a 12 inch length of Tygon tubing. The upper portion of this Mayon tubing was coated with anafoam.

The lower end of the tygon tubing was inserted into a helix. It was held by a rubber stopper which also held a short length of Tygon tubing to allow the escape of excess oxygen.

The helix consisted of Mayon tubing of 1 inch internal diameter. Its lumen was coated with anafoam. The lower end of the helix was stoppered with a rubber stopper, which held Tygon tubing 24 inches in length. This tubing led to the reservoir.

The reservoir consisted of an inverted Kelly flask lined with a plastic bag and stoppered with a rubber stopper which held Tygon tubing connecting it with the helix and the arterial line of Tygon tubing. Two nylon blood filters were placed in the arterial line.

Apparatus III.

The bubbling chamber consisted of Mayon tubing of 2 inch internal diameter. Its lower end held a lucite oxygenator unit containing a perforated nylon plate and a lucite rod for blood delivery as in Apparatus I.

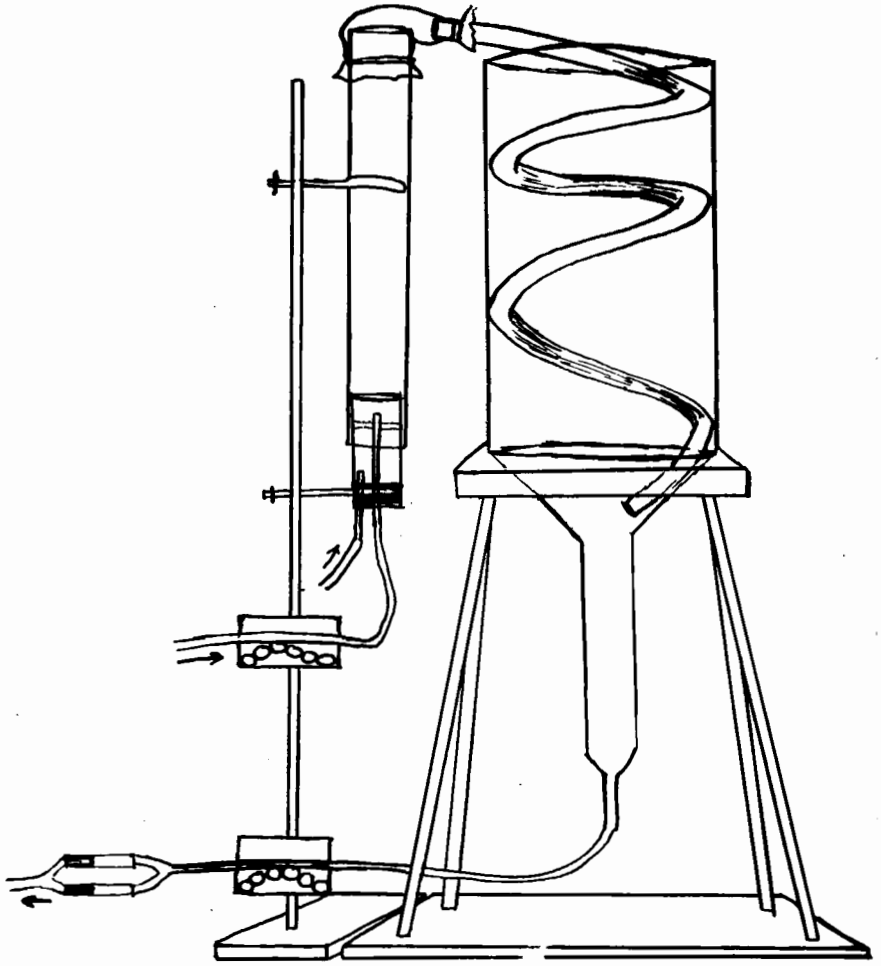

FIGURE XIX

Artificial Oxygenator

Apparatus 3.

The upper end was connected to the helix by a polyethylene cylinder which was fitted over the tubing with rubber bands. This plastic bag was coated with anafoam. The helix was Mayon tubing of 1 inch internal diameter, coated with anafoam. It was placed in a large lucite collecting chamber, see Fig. XIX. The lower portion of this collecting chamber served as a reservoir for the defoamed oxygenated blood. Two nylon filters were placed in the arterial line. The venous and arterial lines were Tygon tubing.

The oxygen was humidified by passing it through a stoppered Kelly flask containing 200 c.c. of water.

Apparatus IV.

This modification was very similar to Apparatus III, except that the upper portion of the bubbling chamber was stoppered. A hole in the upper portion of the wall of the cylinder allowed for insertion of the smaller Mayon tubing of the helix. This was made leak proof by a collar of foam rubber, see Fig. XX.

Method:

The blood recipient dog and donor dogs were cross-matched after the method of Young et al (213). When cross-matching revealed a blood incompatibility between a proposed donor and recipient, the donor dog was not used, and another suitable donor selected.

The donor dogs were anesthetized with nembutal administered intravenously in dosage of 60 mgm. per 5 pounds body weight. The groin was shaved and prepared with 1:1000 zepharin solution. The femoral artery was exposed and cannulated and the blood collected into sterile vacuum bottles, Baxter Laboratories, Morton Grove, Illinois. The vacuum bottles contained 18 mgm. heparin in 50 c.c. of 5 per cent glucose solution for each 500 c.c.

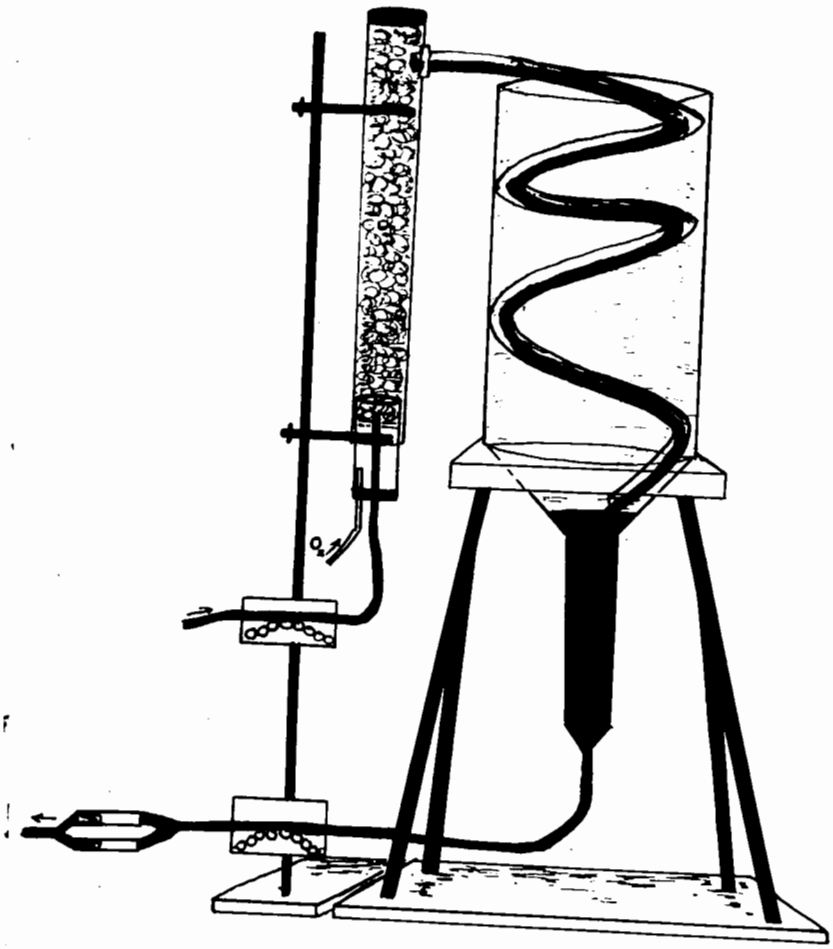


FIGURE XX

Artificial Oxygenator

Apparatus 4.

of blood collected (131).

The patient animal was anesthetized with nembutal administered intravenously, 60 mgm. per 5 pounds body weight. An endotracheal tube was inserted and connected to a mechanical respirator. The animal was postured on the operating table in a supine position and the neck, chest and inguinal regions were shaved and painted with 1:1000 zephiran solution. Electrodes for electrocardiogram tracing were inserted into the limbs. Five per cent glucose was given intravenously into a peripheral vein at 4 to 6 drops per minute.

After suitable draping a vertical incision was made in the groin extending distally from Poupart's ligament to expose the femoral artery. This was cannulated with a fine plastic cannula which was connected to an electromanometer for continuous recording of intra-arterial pressure.

A right thoracotomy incision in the fifth interspace was made in all the experiments but the final one. In the last experiment an anterior trans-sternal incision was made in the fifth interspace in the right chest and the fourth interspace in the left chest thus exposing the anterior portion of the heart and great vessels and both chest cavities.

Heparin, 0.75 mgm. per kilogram body weight, was administered intravenously.

The pericardial sac was incised. A purse string suture of silk was placed in the wall of the right auricular appendage. A #12 French catheter was inserted into the right auricle through a stab wound in the tip of the appendage and guided into the inferior vena cava. The purse string suture was then tied over the catheter to hold it in position. The catheter was allowed to fill with blood and its distal end occluded

with a specially prepared rubber stopper.

A second silk purse string suture was placed in the wall of the right auricle and an incision made in the centre area of the purse string suture. A plastic catheter was placed into the right auricle and guided into the superior vena cava. It was allowed to fill with blood and its distal end was stoppered, Fig. XXI.

The right carotid artery was cannulated with a #12 French plastic catheter, the tip of which was advanced into the ascending aorta.

The extracorporeal circuit was primed with heparinized donor blood. The venous catheters were connected by means of plastic Y tubing to the venous line of the circuit. The arterial catheter was connected with the arterial line of the circuit.

Ligatures, previously placed about the inferior vena cava and superior vena cava were tightened about the catheters to arrest the flow of venous blood to the right auricle, and the pumps were started.

The oxygen flow rate was monitored to obtain optimum bubble formation.

The flow rate of the arterial pump had previously been adjusted to deliver 35 c.c. per kilogram body weight of patient animal per minute. The venous pump was started at this same rate but was constantly monitored during the procedure and its rate adjusted in order to maintain a stationary level in the collecting reservoir.

In 11 experiments an incision was made in the wall of the right ventricle. It was placed about 1/2 inch lateral to the anterior descending branch of the left coronary artery, parallel with it, and was about 2 inches in length. In one experiment an interventricular defect was created. The

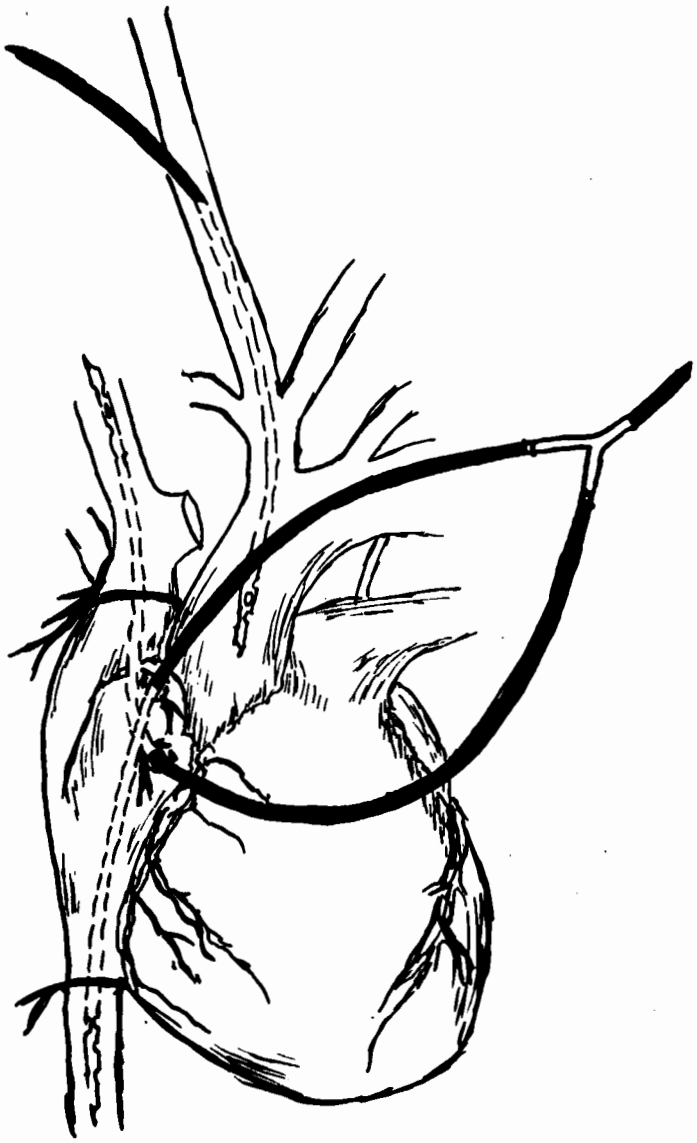

FIGURE XXI

Catheterization of Patient Animal.

edges of the ventricular incision were approximated with continuous 000 silk suture. In one experiment an incision was made in the wall of the right auricle. The incision was approximately 2 inches in length and was placed anterior to the area of insertion of the superior and inferior venae cavae. Its edges were approximated with continuous 000 silk suture.

Perfusion time in the experiments ranged from 12 to 60 minutes. The heart was open for intervals ranging from one to ten minutes. The procedures performed are tabulated in Table I and Table X.

At the conclusion of the cardiac operation the ligatures about the venae cavae were released gradually while the heart was closely observed for overdistension, arrhythmia or cyanosis. Upon release of both venae caval ligatures the perfusion was stopped and the catheters clamped.

During closure of the chest protamine was administered. In the early experiments of this series an arbitrary dose of 50 mgm. of 1 per cent protamine sulfate was given intravenously. In later experiments the protamine was diluted in 200 c.c. of 5 per cent glucose, and given in a slow intravenous drip until the bleeding from the cut surfaces stopped. The protamine dosage in these experiments approximately equaled the heparin dosage.

Post-operatively heparinized whole blood was given as required through a peripheral venous route in order to maintain a good arterial pressure and pulse volume. The chest cavity was aspirated of air and fluid at the conclusion of the operation and at intervals during the post-operative period as indicated.

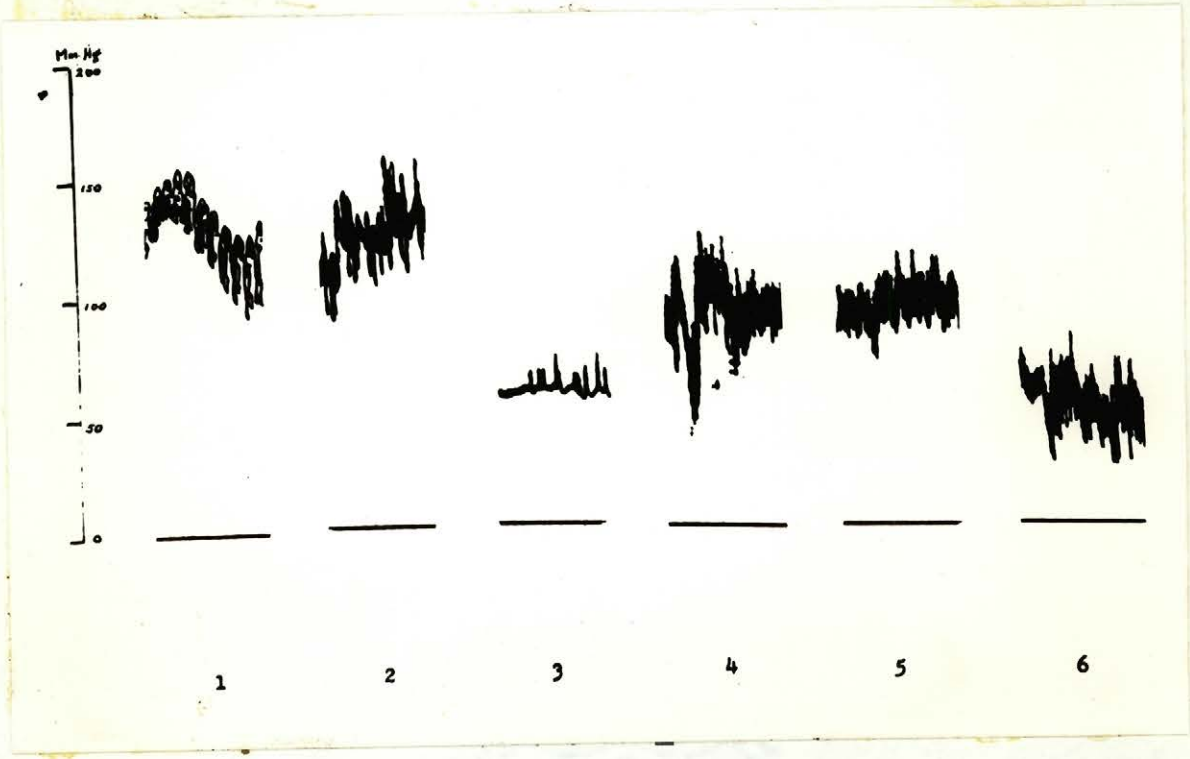


FIGURE XXll

Arterial Blood Pressure Tracing

Artificial Oxygenation

Experiment 55

1. Chest open
2. Perfusion
3. Corporeal circulation re-instituted. Blood 100cc intra-arterial
4. Blood 200cc - anticoagulant EDTA
5. Blood loss in chest cavity
6. Terminal hypotension.

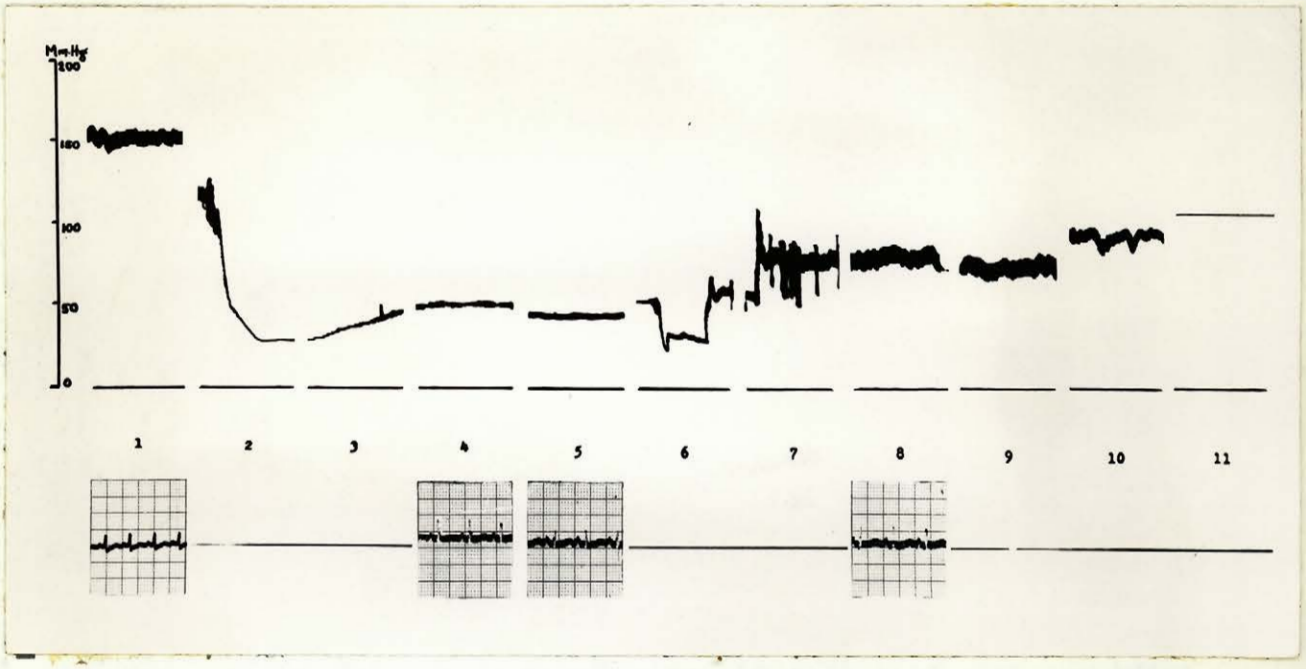


FIGURE XXIII

Arterial Blood Pressure Tracing & Electrocardiogram Lead 11

Artificial Oxygenation

Experiment 61

1. Initial EKG
2. Perfusion
3. Perfusion
4. Perfusion EKG
5. Perfusion EKG
6. Corporeal circulation re-instituted. Blood 100cc intra-arterial
7. Blood 75cc intra-arterial
8. Chest closed EKG
9. Blood 115cc I.V.
10. Chest aspirated
11. Post operative 3 hrs.

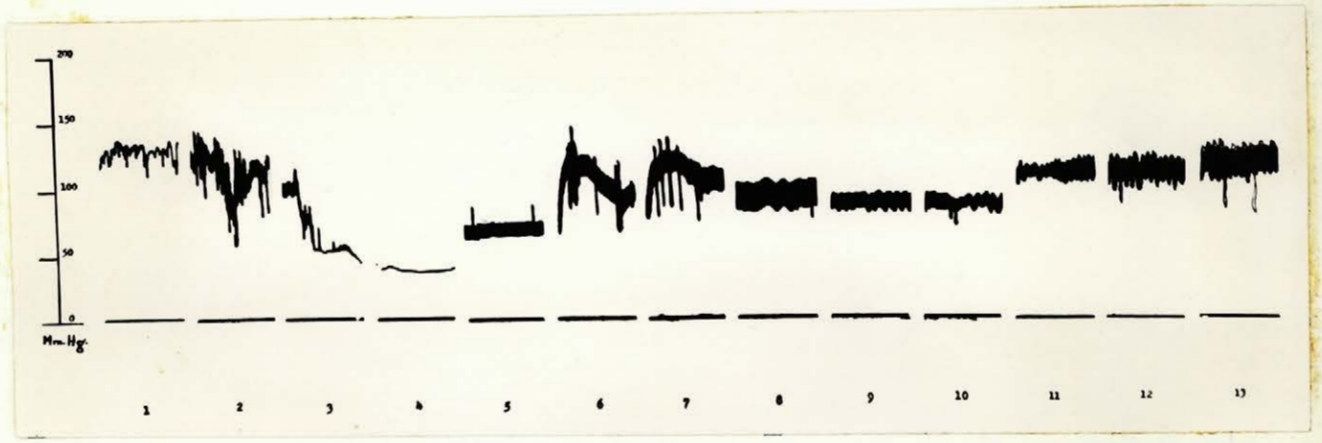


FIGURE XXLV

Arterial Blood Pressure

Artificial Oxygenation

Experiment 59

1. Initial
2. Venous Catheters being placed in heart
3. Perfusion
4. Perfusion
5. Perfusion
6. SVC & IVC released
7. Corporeal circulation
8. Blood pressure stabilized
9. Catheters removed
10. Protamine 32 mgm. in 400cc glucose started I.V. slowly
11. Rectal temp. 37° B.P.rising
12. Blood pressure stable
13. Dog awake and moving.

## Discussion and Results

The oxygenator functioned efficiently. Blood samples taken from the extracorporeal circuit and from the patient animal during perfusion and after perfusion showed oxygen saturation levels well in excess of 90 per cent. The heart appeared well oxygenated during perfusion in the series of experiments. Causes of death are listed in Table X. Ventricular fibrillation occurred in experiment 55. In this experiment ethylene diamine tetra acetic acid (EDTA) was used as the anticoagulant for the donor blood.

Rapid blood loss, possibly from injury to a relatively large pericardial vessel resulted in ventricular fibrillation and an operative death in experiment 58.

In one experiment insufficient heparinization resulted in clotting of blood in the tubing of the extracorporeal circuit and an operative death.

The main complication appeared to be post-operative oozing of blood into the chest cavity. This occurred in spite of meticulous operative procedure and ligation of all bleeding points in the chest wall at operation. Seven late deaths were apparently due to slow post-operative blood loss. At autopsy the amount present in the chest cavity varied between 200 and 500 c.c.

Overtransfusion of 1000 c.c. of heparinized blood in an effort to combat post-operative hypotension accounted for one late death. It is quite possible that rapid protamine administration 50 mgm. of one per cent solution intravenously at the conclusion of the operation was a contributing factor.

Septicemia resulted in death 3 days and 5 days post-operative in experiments 59 and 61 respectively.

Thrombosis of the right auricular appendage extending to fill the entire right auricle appears to have been the cause of death in experiment 61. The thrombus was attached to the stab wound region in the right auricular appendage.

There was no evidence of cerebral damage in the patient animals. The nylon blood filters apparently functioned efficiently. Bjork (17) reported that the use of a Monel metal filter in his artificial oxygenator apparatus reduced the incidence of brain damage in his patient animals.

# CHAPTER VI.

## Discussion of Physiological and Metabolic Changes During Extracorporeal Circulation

### Heparin - Protamine Administration.

Heparin was considered to be the anticoagulant of choice because of its rapidity of action and relatively rapid excretion (94).

It is a mucoitin trisulphuric acid (148), the strongest organic acid known. Its action on blood is antithromboplastic (34) and antithrombic (164).

Anderson and Fawcett (2), in 1950 noted that the injection of heparin 50 mgm. intravenously in the human caused a sudden fall of surface tension and a clearing of lipemic plasma. The activity appeared to be due to the formation of a surface active heparin-phospholipid complex. The highly acid heparin molecule was probably attached to the extremely basic choline of a phospholipid similar to lecithin which had a theoretical iso-electric point of pH 7.5.

Bell, (11) in 1951, observed a coagulation defect in a human patient due to an anticoagulant possessing antithromboplastic and antithrombic properties, probably heparin. Protamine sulfate 200 mgm. when administered intravenously, reduced the clotting time from 106 to 43 minutes.

Heparin dosage in our experiments varied between 0.75 mgm. per kilogram body weight and 1.5 mgm. per kilogram body weight.

Donor blood was heparinized by two methods. In some experiments the donor animal was given heparin in dosage as stated above. In the remaining experiments the donor animal was not heparinized, but the blood was collected in Baxter Transfuso Vac bottles to which heparin had been

added. Dosage varied between 10 mgm. and 20 mgm. for each 500 c.c. of blood collected.

In the artificial oxygenation series the heparin 18 mgm. was diluted in 50 c.c. of 5 per cent glucose for each 500 c.c. of donor blood (131).

In experiment 55 the donor blood was collected in 3 plastic collecting bags containing ethylene diamine tetra acetic acid (EDTA) as the anticoagulant. Blood clots were noted in the tubing of the extracorporeal circuit after only a few minutes perfusion.

Protamine was administered in 22 experiments.

Chargoff (26) reported that the anticoagulant effect of heparin was destroyed by salmine. Salmine itself was known to be an anticoagulant. Protamine and heparin combined in proportion of 0.3 mgm. heparin to 1 mgm. protamine, and in this state the anticoagulant action of heparin disappeared.

Vartianen et al. (198) in 1941 noted a fall in blood pressure in the experimental animal after injection of protamine. When the dosage was insufficient to produce fatality, the blood pressure returned to normal in 25 to 30 minutes.

Stokes et al. (187), in 1950, in their experiments on extracorporeal circulation, used 1 mgm. protamine per mgm. heparin given, and found that when protamine was given rapidly or in concentrations greater than 0.025 per cent, a fall in arterial blood pressure to 40 to 60 mm. mercury consistently occurred. When the same amount of protamine in dilute solution was administered over a 10 minute period no drop in blood pressure or other undesirable effects were noted.

Hurt (91) in 1956, reported that protamine, after heparin administration and extracorporeal circulation may produce an increase in clotting time if given in excess.

In the early experiments in our series an empirical dose of 50 mgm. of one per cent solution was given intravenously. In experiment 50, the protamine dosage was 120 mgm. and in experiment 56, 100 mgm. of 1 per cent solution of protamine was administered.

In the group of 19 experiments in which protamine was given in dosage of 50 mgm. or greater in one per cent solution, post-operative bleeding was a major complication in 9 experiments.

In experiments 59, 61 and 62 the protamine was diluted to less than 0.025 per cent dilution in normal saline or 5 per cent glucose, and given slowly in an intravenous drip. Protamine-heparin titration (124) was carried out in the last 10 experiments. The total dosage of protamine administered was about equal to the amount of heparin given.

There was some blood loss post-operatively but the amount was considerably less than in previous experiments, and, in none of these experiments was bleeding the cause of death of the patient animal.

We cannot show a definite relation in our experiments between post-operative hypotension and the administration of heparin. However, in the series with artificial oxygenation the post-operative hypotension occurred only in those animals in which a dose of 50 mgm. or more of protamine was administered in one per cent solution.

In experiments 59, 61 and 62 the protamine was given slowly in diluted form, and the post-operative arterial pressures were 120, 110 and 100 mm. mercury respectively.

TABLE IV

(HEPARIN-PROTAMINE DOSAGE)

| Exp. No. | Type of Oxygenation | Total Heparin Dosage mgm. | Total Protamine Dosage mgm. | Dilution of Protamine % | Arterial Systolic B.P. During Occlusion of venae cavae | Arterial Systolic B.P. at Conclusion of Operation | Survived (s) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 1 | cross circulation | 40 | 0 | | | | | Bilateral atelectasis Blood loss |
| 4 | cross circulation | 27.5 | 0 | | | | S | |
| 5 | cross circulation | 30 | 0 | | | | S | |
| 6 | lung | 25 | 0 | | | | | Blood loss |
| 7 | lung | 22 | 0 | | | | S | |
| 8 | lung | 35 | 0 | | | | S | |
| 9 | lung | 40 | 0 | | | | | Ventricular fibrillation |
| 10 | lung | 0 (citreted) | 0 | | 40-140 | 40 | | Air emboli |
| 13 | lobe | 25 | 0 | | | | | Air emboli |
| 14 | lobe | 35 | 0 | | | | | Ventricular fibrillation |
| 15 | lobe | 32.5 | 50 | 1 | | | | Blood loss |
| 20 | lung | 60 | 50 | 1 | | | S | |
| 23 | lung | 60 | 50 | 1 | | | S | |

TABLE IV, Continued

| Exp. No. | Type of Oxygenation | Total Heparin Dosage mgm. | Total Protamine Dosage mgm. | Dilution of Protamine % | Arterial Systolic B.P. During Occlusion of venae cavae | Arterial Systolic B.P. at Conclusion of Operation | Survived (S) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 24 | lung | 60 | 50 | 1 | | | | Empyema Septicemia |
| 25 | lung | 57.5 | 50 | 1 | | | | Brachio cephalic artery divided |
| 27 | lung | 65 | 50 | 1 | | | | Brachio cephalic artery divided |
| 28 | lung | 90 | 0 | | | | | Brachio cephalic artery divided |
| 29 | lung | 50 | 0 | | | | | Blood loss |
| 30 | lung | 50 | 0 | | | | | Brachio cephalic artery divided |
| 31 | lung | 75 | 50 | 1 | 35 | 100 | | Brachio cephalic artery divided |
| 32 | lung | 75 | | | 45-20 | 35 | | Brachio cephalic artery divided |
| 33 | lung | 75 | 50 | 1 | | 120 | | Brachio cephalic artery divided |
| 34 | lung | 75 | 50 | 1 | 25-20 | 60 | | Brachio cephalic artery divided |
| 37 | lung | | | | 40-50 | 80 | | Distemper |
| 38 | lung | | 50 | 1 | | 60 | | Blood loss |
| 39 | lung | 43 | 0 | | 40 | 85 | S | |
| 40 | lung | 51.5 | 50 | 1 | | 90 | | Blood loss |
| 43 | artificial | 34.5 | 0 | | | | | Blood loss |
| 44 | artificial | | 50 | 1 | | | | Blood loss |

TABLE IV. Continued

| Exp. No. | Type of Oxygenation | Total Heparin Dosage mgm. | Total Protamine Dosage mgm. | Dilution of Protamine % | Arterial Systolic B.P. During Occlusion of venae cavae | Arterial Systolic B.P. at Conclusion of Peration | Survived (s) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 45 | artificial | 45 | 50 | 1 | 65-30 | 100 | | Blood loss |
| 46 | artificial | 20.5 | 50 | 1 | 40-60 | 100 | | Atelectasis |
| 47 | artificial | 48.5 | 0 | | | 120 | | Blood loss |
| 49 | artificial | 72.5 | 50 | 1 | 40 | 60 | | Overtransfusion |
| 50 | artificial | 30.5 | 120 | 1 | 10-20 | 20 | | Blood loss |
| 52 | artificial | 31 | 0 | | | | | Blood clotted in tubing |
| 53 | artificial | 46 | 50 | 1 | 20-40 | 60 | | Blood loss |
| 54 | artificial | 40+ | 50 | 1 | 20-40 | 40 | | Blood loss |
| 55 | artificial | 11 EDTA | 0 | | 40 | 60 | | Blood clots in tubing |
| 56 | artificial | 42 | 100 | 1 | 40-50 | 90 | | Blood loss |
| 58 | artificial | 45 EDTA | 0 | | | | | Ventricular fibrillation Blood loss |
| 59 | artificial | 47 | 35.2 | 0.017 | 40-60 | 120 | | Septicemia |
| 61 | artificial | 40 | 48 | 0.014 | 60 | 110 | | Pericarditis, blood loss |
| 62 | artificial | 55 | 45 | 0.026 | | 100 | | Thrombosis right auricle, Blood loss |

In experiment 60 the arterial blood pressure in dogs was measured after administration of heparin and protamine. Six dogs were anesthetized with sodium pentothal given intravenously.

Dog No. 1 received 50 mgm. of heparin intravenously, and, a few minutes later, 50 mgm. of protamine in one per cent solution, also intravenously. A definite fall in arterial blood pressure occurred. This did not rise to control level, Fig. XXV.

Dog No. 2 received the same dosage of heparin and protamine in the same concentration as dog No. 1, but showed only a slight fall in blood pressure, Fig. XXVI.

Dog No. 3 received protamine 50 mgm. diluted in 200 c.c. of 5 per cent flucose and showed only a slight fall in blood pressure, which rapidly rose to control level with slowing of the intravenous drip of protamine from 60 to 14 drops per minute, Fig. XXVII.

Dogs No. 5 and 6 received protamine only, 50 mgm. in one per cent solution, and showed a transient drop in blood pressure which rose to control level, Fig. XXVIII.

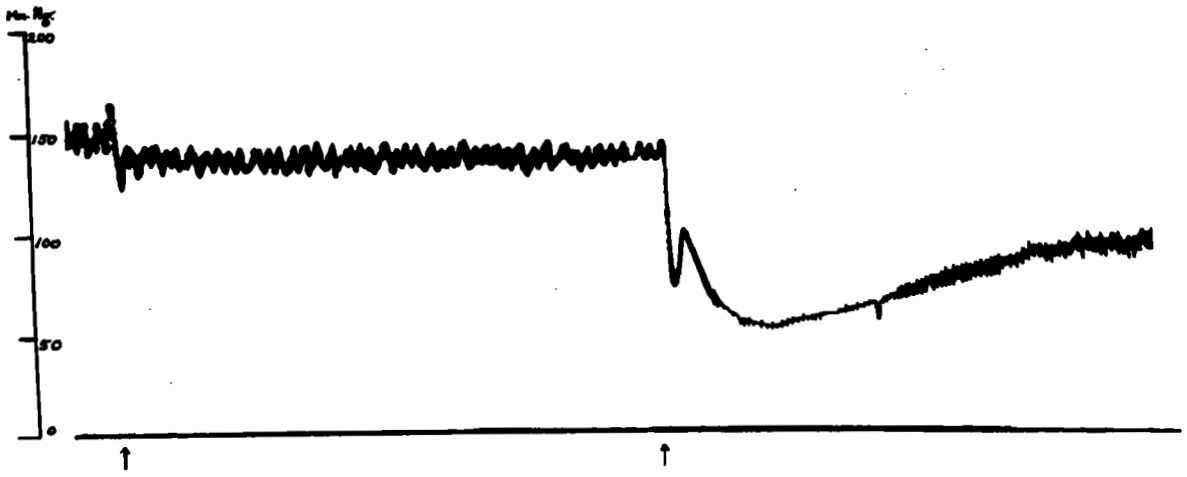


FIGURE XXV

Arterial Blood Pressure

Experiment 60

Heparin 50 mgm. intra-arterially

Protamine 50 mgm. intra-venously in 1% solution.


FIGURE XXVI

Arterial Blood Pressure

Experiment 60

Heparin 50 mgm. intra-venously

Protamine 50 mgm. intra-venously in 1% solution.

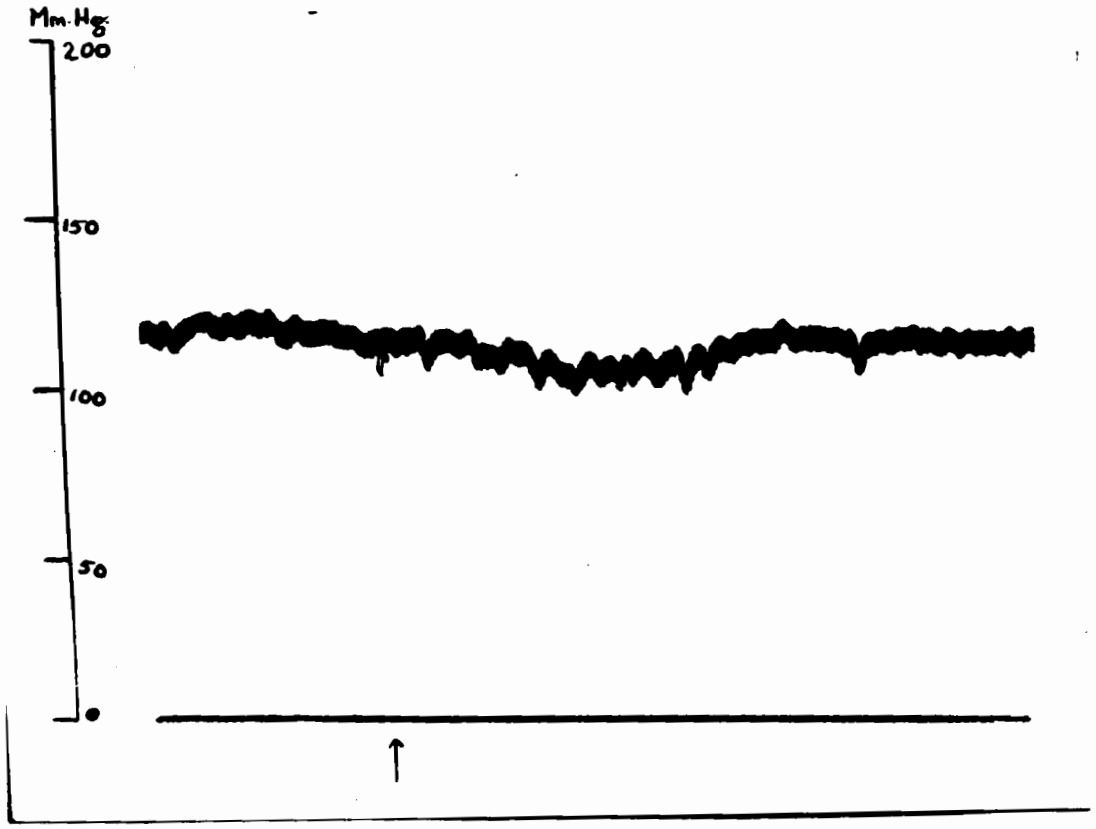


FIGURE XXVIII

Arterial Blood Pressure

Experiment 60

Protamine intra-venously 50 mgm. in 200cc glucose.

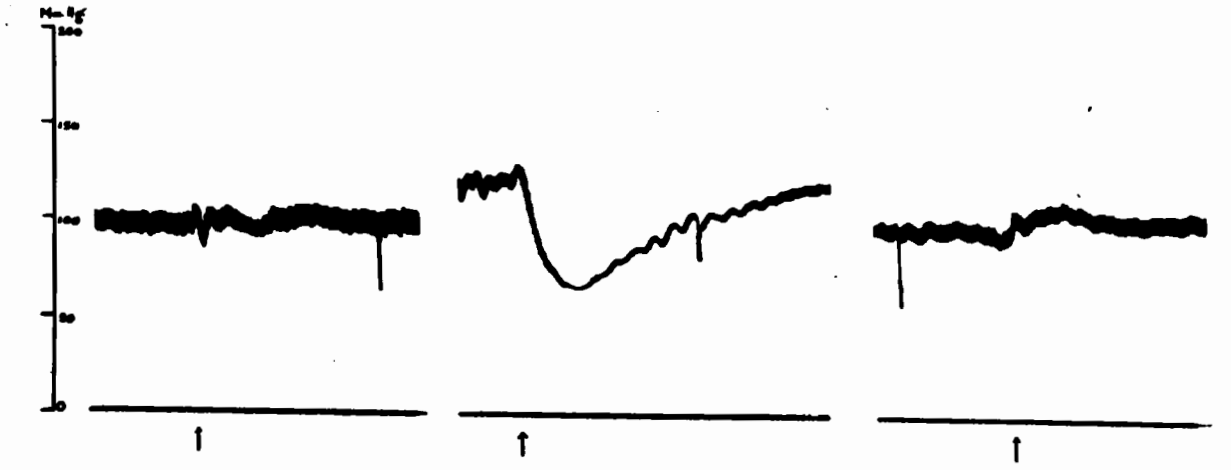

FIGURE XXVIII

Arterial Blood Pressure

Experiment 60

Initial B.P.

Protamine 50 mgm. intra-venously in 1% solution.

Rise in B.P. to almost control level.

## Blood Oxygen Saturation

Blood oxygen saturation (176) was excellent in all experiments when measurements were taken. Values were consistently above 90 per cent as tabulated in Tables V. and VI.

Venous oxygen content specimens were taken in experiments 29 and 30. Both experiments illustrated an increase in coefficient of oxygen utilization in that the final venous blood oxygen levels were considerably reduced over control levels.

### Carbon Dioxide Content of the Blood:

There was no evidence of marked rise in carbon dioxide (197) content of the blood in any of the specimens taken, as shown in Table VII.

### pH of the Blood:

There was no undue change from control pH values in the specimens taken. Experiment 47 in Table VIII. illustrates the value of inflation of the lungs of the patient animal during perfusion in maintaining the pH near control levels.

### Red Blood Cell Fragility:

Table IX shows values of red blood cell fragility taken in 2 experiments only. All values were within normal range (210).

### Blood Calcium:

Blood calcium determinations (210) were done in experiments 55 and 56 after the administration of calcium chloride to the patient animal. All specimens showed increased calcium levels varying from 14 mgm. per cent to 29 mgm. per cent.

### Platelet Count:

Platelet counts (210) were taken in experiments 33 and 39. All values were within normal limits before and after perfusion.

TABLE V

| Exp. No. | BLOOD OXYGEN CONTENT OXYGEN SATURATION PER CENT Contral Arterial | Contral Venous | BIOLOGICAL LUNG OXYGENATION Final Arterial | Final Venous | Perfusion Time Min. |
|---|---|---|---|---|---|
| 10 | | | 90 | | 2 |
| | | | 91.5 | | 4 |
| 12 | | | 100 | | 8 |
| | | | 100 | | 24 |
| | | | 99.5 | | 35 |
| 14 | | | 93.6 | | 7 |
| | | | 99.7 | | 15 |
| 27 | 22.39 V01% | | | | |
| | | | 15.24 V01% | | |
| 29 | | 19 | | | |
| | | 7.6 | | | |
| | | | 97 | | |
| 30 | 97 | | | | |
| | | 23.2 | | | |
| | | | 100 | | |
| | | | | 5.94 | |
| 31 | 100 | | | | |
| | | 13.0 | | | |
| | | | 100 | | |
| | | | | 18.5 | |
| 39 | 100 | | | | |
| | | | 90.5 | | |

TABLE VI

| BLOOD OXYGEN CONTENT | | ARTIFICIAL OXYGENATION | |
|---|---|---|---|
| | OXYGEN SATURATION PER CENT | | |
| Exp. | Control | Final | |
| No. | Arterial Venous | Arterial Venous | Perfusion Time Min. |
| 42 | | 93.7 | 45 |
| | | 100 | 60 |
| 45 | | 80.5 | 10 |
| | | 98 | 30 |
| 47 | 100 | | |
| | | 93.5 | |

TABLE VII

BLOOD CARBONDIOXIDE CONTENT — BIOLOGICAL LUNG OXYGENATION

CARBON DIOXIDE SATURATION VOLUMES PER CENT

| Exp. No. | Contral Arterial | Contral Venous | Final Arterial | Final Venous | Perfusion Time |
|---|---|---|---|---|---|
| 14 | | | 33.61 | | 7 |
| | | | 34.4 | | 15 |
| 27 | 28.42 | | | | |
| | | | 41.9 | | |
| 29 | | 43.5 | | | |
| | | | | 45.7 | |
| | | | 31.15 | | |
| 30 | | 39.5 | | | |
| | | | 31.8 | | |
| | | | | 41.4 | |
| 31 | 22.18 | | | | |
| | | 40.14 | | | |
| | | | 16.56 | | |
| | | | | 33.02 | |

TABLE VIII

pH VALUES WITH EXTRA CORPOREAL OXYGENATION

| Exp. No. | | Lung Oxygenator | Articial Oxygenator |
|---|---|---|---|
| 29 | Initial | 7.27 | |
| | Conclusion of operation Pt. lung not respirated during extra corporeal circulation | 7.39 | |
| 47 | Donor blood-control | | 7.390 |
| | Patient blood-arterial control | | 7.5020 |
| | ft. blood after 20 min. extra corporeal circulation and pt. lungs not inflated | | 7.357 |
| | Pt. blood 10 min. later extra corporeal circulation and pt. lungs inflated 10 min. | | 7.525 |
| 48 | Perfusion only of human citrated blood 26 days old | | |
| | 1. control | | 6.275 |
| | 2. 20 min. perfusion | | 6.661 |
| | 3. 40 min. perfusion | | 6.678 |

TABLE IX

RED BLOOD CELL FRAGILITY WITH ARTIFICIAL OXYGENATION

| Exp. No. | | ARTIFICIAL OXYGENATOR | | |
|---|---|---|---|---|
| | | Initial | Complete | Incomplete |
| 42 | 1. Control | 55 | 40 | |
| | 2. 15 min. perfusion | 55 | 35 | |
| | 3. 30 min. perfusion | 55 | 35 | |
| | 4. 45 min. perfusion | 55 | 35 | |
| 49 | 1. Control | | | 50 |
| | 2. 12 min. perfusion | | | 50 |

Hemolysis:

Plasma hemoglobin determinations (15) were performed in 10 experiments. The highest tabulated value obtained in centrifuged specimens in perfusion experiments was 0.449 gm. per cent hemoglobin.

Hematocrit (210) values were taken in experiments 46 and 49 and in experiment 46 showed a drop from 49 control to 38, while experiment 49 showed a drop from a control reading of 40.4 to a post-perfusion reading of 37.9 per cent.

Fibrinogen Content:

Fibrinogen determinations (152) were performed in experiments 51 and 59. Values of a control of 0.225 gm. per cent a 30 minute perfusion reading of 0.231 gm. per cent in experiment 51, and a post-operative reading of 0.1936 gm. per cent in experiment 59 were obtained. All are within normal limits.

Thus, there was no evidence of change outside the physiological range in oxygen content, carbon dioxide content, red blood cell fragility, platelet count, fibrinogen, hemolysis of red blood cells and hematocrit in the specimens tested.

TABLE X

OPERATIVE RESULTS

| Exp. No. | Cause of Operative Death | Cause of Post Operative Death | Survival time | Type of Oxygenation | Intracardiac Procedure |
|---|---|---|---|---|---|
| 1. | | Bilat-pneumethorax Bilat atelectosis Blood loss | 2 hr. | X circ. | |
| 2. | | Blood loss | 1 d. | Hypothermia | |
| 3. | | Sacrificed | 5 wks. | Hypothermia | |
| 4. | | Sacrificed | 1 mo. | X circ. | |
| 5. | | Sacrificed | 3 wks. | X circ. | IASD & repair |
| 6. | | Blood loss Incompatible transfusion. Donor dog previously cross transfused | 3 hr. | Lung | IASD & repair |
| 7. | | Sacrificed | 1 mo. | Lung | IASD & repair |
| 8. | | Air emboli in coronary arteries | 12 hr. | Lung | IASD & Repair |
| 9. | | Sacrificed | 5 wks. | Lung | Cardiotomy Rt. auricle |
| 10. | Cardiac arrest air emboli | | | Lung | Cardiotomy Rt. auricle |
| 13. | Ventricular fibrillation Coronary air emboli | | | Lung | Cardiotomy Rt. ventricle |
| 14. | Ventricular fibrillation | | | Lung | Cardiotomy Rt. ventricle |
| 15. | | Blood loss | 48 hr. | Lung | Cardiotomy Rt. ventricle |
| 16 | | Sacrificed | 1 mo. | Hypothermia | Cardiotomy Rt. Ventricle |
| 17. | Cardiac arrest | | | Hypothermia | IVSD & repair |
| 22. | | Sacrificed | 3 wks. | Lung | Cardiotomy Rt. auricle |

TABLE X, Continued

| Exp. No. | Cause of Operative Death | Cause of Post Operative Death | Survival Time | Type of Oxygenation | Intracardiac Procedure |
|---|---|---|---|---|---|
| 23. | | Sacrificed | 3 wks. | Lung | Cardiotomy Rt. ventricle |
| 24. | | Empyema Septicemia | 15 ds. | Lung | Cardiotomy Rt. Ventricle |
| 25. | | Brachio cephalic artery divided | 12 hr. | Lung | Cardiotomy Rt. Ventricle |
| 27. | | Brachio cephalic artery divided | 12 hr. | Lung | Cardiotomy Rt. ventricle |
| 28. | Ventricular fibrillation | | | Lung | Cardiotomy Rt. ventricle |
| 29. | | Blood loss | 12 hr. | Lung | Cardiotomy Rt. ventricle |
| 30. | Cardiac arrest Brachio cephalic artery divided | | | Lung | Cardiotomy Rt. ventricle |
| 31. | | Brachio cephalic artery divided Blood loss | 36hr. | Lung | Cardiotomy Rt. ventricle |
| 32. | Ventricular fibrillation | Brachio cephalic artery divided | | Lung | Cardiotomy Rt. ventricle |
| 33. | | Brachio cephalic artery divided | 24 hr. | Lung | Cardiotomy Rt. ventricle |
| 34. | | Brachio cephalic artery divided | 12 hr. | Lung | Cardiotomy Rt. ventricle |
| 35. | | Brachio cephalic artery divided | 24hr. | Lung | Cardiotomy Rt. ventricle |
| 36. | | Brachio cephalic artery divided | 24 hr. | Lung | Cardiotomy Rt. Ventricle |
| 37. | | Distemper Pneumonia | 48 hr. | Lung | Cardiotomy Rt. ventricle |
| 38. | | Blood loss | 2 hr. | Lung | Cardiotomy Rt. ventricle |
| 39. | | | | Lung | Cardiotomy Rt. ventricle |

TABLE X. Continued

| Exp. No. | Cause of Operative Death | Cause of Post Operative Death | Survival Time | Type of Oxygenation | Intracardiac Procedure |
|---|---|---|---|---|---|
| 40. | | Blood loss | 12 hr. | Lung | Cardiotomy Rt. ventricle |
| 43. | | Blood loss | 12 hr. | Artificial | Cardiotomy Rt. ventricle |
| 44. | | Blood loss | 12hr. | Artificial | Cardiotomy Rt. ventricle |
| 47. | | Blood loss | 12 hr. | Artificial | IVSD |
| 49. | | Overtransfusion | 6 hr. | Artificial | Cardiotomy Rt. ventricle |
| 50. | | Blood loss Atelectoses | 2½hr. | Artificial | Cardiotomy Rt. ventricle |
| 52. | Ventricular fibrillation clotting of blood | | | Artificial | Cardiotomy Rt. ventricle |
| 53. | | Blood loss | 12hr. | Artificial | Cardiotomy Rt. ventricle |
| 54. | | Blood loss | 6hr. | Artificial | Cardiotomy Rt. auricle |
| 55. | Ventricular fibrillation EDTA anticoagulant | | | Artificial | Cardiotomy Rt. ventricle |
| 56. | | Blood loss | 12hr. | Artificial | Cardiotomy Rt. ventricle |
| 58. | Ventricular fibrillation Blood loss | | | Artificial | Cardiotomy Rt. Ventricle |
| 59. | | Septicemia | 3 d. | Artificial | none. |
| 61. | | Septicemia Blood loss | 5 d. | Artificial | none. |
| 62. | | Thrombus in rt. auricle blood loss | 60hr. | Artificial | Cardiotomy Rt. ventricle |

## CHAPTER VII.

### Survival and Cause of Death

In the homologous lung oxygenation group there were five long term survivals. All appeared normal in every way. Four of these were sacrificed approximately one month post-operatively, and, at autopsy were normal in every way. The cardiotomy incisions were well healed.

There were six operative deaths in this group (see Table XI.). Two were the direct result of technical error and coronary air emboli. Ventricular fibrillation in experiment 28 was precipitated by anoxia of the myocardium. It is possible that the arterial catheter tip had not been advanced far enough into the ascending aorta to supply the coronary arteries adequately.

Two operative deaths were due to division of the brachio-cephalic artery.

Late deaths in the homologous lung series were due in 6 experiments to blood loss. Incompatible blood transfusion may have been a contributing factor in the early experiments, as donor blood was taken from dogs sacrificed after transfusion.

One late death was apparently due to air emboli in the coronary arteries as a result of technical error.

Post-operative infection resulted in late death of the patient animal in two experiments.

Erroneous division of the brachio-cephalic artery resulted in death within 24 hours in 8 experiments.

In the artificial oxygenation series there were three operative deaths (see Table X.). One was due to insufficient heparinization and

clotting of blood in the tubing of the extracorporeal circuit.

Ethylene diamine tetra acetic acid (EDTA) was used as the anticoagulant for the donor blood in experiment 55. Ventricular fibrillation occurred. Calcium chloride was administered at the time with no effect.

Rapid blood loss, possibly from a relatively large pericardial vessel resulted in ventricular fibrillation and an operative death in experiment 58.

Late deaths, in the artificial oxygenation series, were due to post-operative oozing into the chest cavity in 7 experiments (see Table XI.). At autopsy the amount present in the chest cavity varied between 200 and 500 c.c.

Overtransfusion of 1000 c.c. of heparinized blood in an effort to combat post-operative hypotension unsuccessfully accounted for one late death. It may be that rapid protamine administration, 50 mgm. of 1 per cent solution intravenously at the conclusion of the operation was a contributing factor.

Septicemia resulted in death 3 days and 5 days post-operative in experiments 59 and 61 respectively.

Thrombosis of the right auricular appendage extending to fill the entire right auricle appears to have been the main cause of death in experiment 61. The thrombus was attached to the stab wound region in the right auricular appendage.

TABLE XI

SURVIVAL AND CAUSE OF DEATH

| | CONTROLLED CROSS CIRCULATION | HOMOLOGOUS LUNG OXYGENATOR LOBE OXYGENATOR | LUNG OXYGENATOR | ARTIFICIAL OXYGENATOR |
|---|---|---|---|---|
| Total Number of Operations | 3 | 3 | 23 | 16 |
| Thoracotomy only | | | | 3 |
| Right Auriculotomy | 2 | 0 | 3 | 1 |
| IASD & repair | 1 | 0 | 2 | |
| Right Ventriculotomy | 0 | 3 | 18 | 11 |
| IVSD | | | | 1 |
| Survivals | 2 | 0 | 5 | 0 |
| Deaths | 1 | 0 | 18 | 16 |
| Causes of Death | (1) Blood loss and Atelectasis | (1) Airemboli<br>(1) Ventricular fibrillation<br>(1) Blood loss | (4) Blood loss.<br>(1) Ventricular fibrillation<br>(1) Air emboli and failure of donor lung<br>(10) Brachio cephalic artery divided<br>(1) Empyema and Septocemia<br>(1) Distemper and Pneumonia | (8) Blood Loss<br>(2) Bilateral Atelectasis and Blood loss<br>(1) Pericarditis and Blood loss<br>(1) Thrombosis Rt. Auricle and Rt. Ventricle and Blood loss<br>(2) Blood clots in extra corporeal circuit<br>(1) Overtransfusion<br>(1) Septicemia |

## CHAPTER VIII.

### Summary and Conclusions

Three techniques of extracorporeal circulation were investigated.

Three experiments involving controlled cross-circulation were performed with two long term survivals of the patient animals and three long term survivals of the donor animals.

Twenty-six operative experiments utilizing homologous lung oxygenation were performed, with five long term survivals.

Sixteen operative experiments with artificial extracorporeal oxygenation were performed with no long term survivals, but with only three operative deaths. Nine animals succumbed within twelve hours post-operative.

Three animals survived 2 1/2 days, 3 days and 5 days respectively.

Perfusion experiments were performed with homologous lung oxygenation with control of endotracheal pressure and pulmonary artery pressure in the donor lung.

Controlled intermittent positive pressure and intermittent negative pressure respiration methods were investigated.

Positioning of the donor lung, upright in some experiments, and in the inverted position in other experiments, for more adequate endotracheal drainage was investigated.

Perfusion substances of the donor lung were tested and observations made on microscopic changes. Dextran, plasma and blood were found least likely to cross the capillary wall barrier into the alveoli.

In all experiments with homologous lung oxygenation the arterial blood was almost fully saturated in all specimens taken.

Four modifications of the artificial oxygenation apparatus were investigated. All were based on the principle of mechanical mixing by bubbling oxygen through blood. Anafoam (DC antifoam A) was used full strength and in dilution with ether in coating the inner surface of the defoaming chamber.

Various doses of heparin were investigated in both the patient animal and in the donor blood.

Protamine was used in the majority of the artificial oxygenation experiments. In the early experiments it was given rapidly intravenously in one per cent solution. In later experiments the protamine was given slowly in dilution with glucose and attempts at heparin-protamine titration were made using the clotting time as a guide.

Blood oxygenation was excellent in all experiments with the artificial oxygenator.

There were no changes outside the physiological range in any specimens taken for investigation of blood pH, platelet count, red blood cell fragility, fibrinogen, hemolysis of red blood cells and hematocrit determination.

It is the opinion of our group that all three techniques of extra corporeal circulation investigated, that is, controlled cross-circulation, biological lung oxygenation and artificial oxygenation have possibilities for clinical use for open cardiac surgery, but that more research of an explicit nature in investigating physiological and metabolic changes associated with these techniques must be done.

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