THE EFFECTS OF MEMBRANE OXYGENATION
DESIGN ON OXYGENATION PERFORMANCE & BLOOD DAMAGE.

A THESIS SUBMITTED FOR THE DEGREE OF

MASTER OF PHILOSOPHY.

by

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SUMMARY.

The superiority of the membrane oxygenator over its gas contacting counterpart in minimizing blood trauma is not considered proved. To this end a model membrane oxygenator and perfusion circuit were designed to test ways of improving gas transfer and comparing the hemolysis and protein denaturation caused by the two types of artificial lung. Experiments used human transfusion blood at physiological temperature and gas tensions.

From data gained and from the 1,000 papers reviewed, membrane oxygenator design criteria were produced.

A theoretical analysis of the gas transfer across the membrane suggested that the active vibration of the oxygenator effectively eliminated the resistance of the plasma to gas flow.
ACKNOWLEDGMENT.

I would like to express my gratitude to Dr. J. Edwards, my Supervisor, and Reader in Biomechanics at the University of Surrey, for initially stimulating, continually guiding and encouraging my endeavours in bioengineering.
TO MY WIFE AND PARENTS

Without whose help and co-operation

this work would not have been possible.
PREFACE.

"Of artificial systems the most attractive is that where in imitation of the natural pulmonary anatomy, a membrane separates blood from gas."

"Heart lung machines have been described as a string of blood smashing devices in series with a protein denaturation attachment."

Longmore 1968.

The above quotes summarise the promise and problems of the modern artificial lung. The ability to produce thin silicone rubber sheet has made the membrane oxygenator a viable machine and heralds a solution to a whole new range of clinical problems. However, the benefits of membrane devices are felt rather than proved, their designs vary widely and their efficiencies are low.
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1.1 Introduction.

In 1952, Dr. Gibbon operated on an eighteen-year-old girl who had developed a hole in the heart wall which separates the atria. For 26 minutes surgeons worked to seal the hold, while a machine pumped and oxygenated the girl's blood. The operation was a complete success.

The heart-lung machine, comprising a pump and an oxygenator, is now a highly dependable, everyday piece of surgical equipment. However, the discovery of a method of producing thin membrane sheet enabling machines to be constructed which mimic the lung's method of oxygenating blood heralded a whole new range of possibilities for the heart-lung machine.

This thesis explores some of the problems involved in perfecting such a modified oxygenator and reviews a wide range of recent work in this field.
1.2 The Function of an Oxygenator.

In an oxygenator, venous blood gives up its carbon dioxide in exchange for a fresh supply of oxygen. A better name for it might be an 'artificial lung' or a 'gas exchanger'.

To understand what is required of such a device, it is best to look at what it has to replace - the lungs. The total useful area of each pair of lungs is 50 - 70 m², about equal to the ground floor area of an average house. The 750 million alveoli of the lungs are enclosed in a fine mesh of capillaries only 5 - 10 µ in diameter, but whose length totals several hundred kilometres. At any one time, these capillaries contain 70 - 80 ml of blood and since the capillary walls and their endothelial lining are each only 0.1 µ thick, diffusion takes place through a barrier only 2 µ thick.

In spite of their narrowness and length, the capillaries only require about 100 mm Hg pressure to maintain a 5 l/min flow rate. Even during exertion when blood flow quadruples to 20 l/min, the pressure only rises to 20 mm Hg.

The average time spent by a red cell in the lung is 0.75 s at rest and 0.33 s during exertion. Since it only takes a red cell one millisecond to establish equilibrium with its surroundings there is more than sufficient time for efficient gas exchange.

At rest, the body must eliminate 0.25 l/min. of carbon dioxide and take in 0.25 l/min. of oxygen, while during exertion these figures may rise to 5.5 l/min. - still well short of maximum capacity.
To summarise, the lung has a vast area of ultra thin membrane in intimate contact with a tiny amount of blood which flows quickly in and out of the capillaries under minimal pressure. Were we required to mimic the capability, the task would be hopeless. Fortunately, though, three factors are on our side:

1. In bypass surgery, we need only support the body at rest. This requires a blood flow rate of 5 l/min. and a gas transfer rate of 0.25 l/min.

2. We can replace air which contains 20% oxygen with 100% oxygen to greatly increase the partial pressure gradient.

3. The lung has so much spare capacity to meet the 'at rest' requirements that only 1.8 m² of its total area would be necessary.

1.3 Types of Oxygenator.

In artificial lungs, a large surface for gas exchange is obtained either by dispersion of the gas in blood as a bubble or foam oxygenators or by dispersion of blood in the gas, as in spray and film oxygenators. The latter requires a blood film to be maintained continuously either by running the film down a stationary screen or surface, or by a moving disc or drum. The third major category covers membrane oxygenators in which the blood and gas phases are separated by a gas-permeable membrane to eliminate trauma caused by a raw blood-gas interface.

1.3.1 Bubble Oxygenators.

In the bubble oxygenator, gas is dispersed upward through the venous blood film from holes in the gas manifold, and gas exchange takes place during this ascent. The remaining foam is eliminated by 'antifoam' surfaces, settling, trapping, filtration or centrifuging. Bubble size is a crucial factor in a three way compromise between minimising hemolysis (red cell damage), giving sufficient oxygen to the blood and removing the correct proportion of carbon dioxide from it.

Bubble oxygenators are claimed to cause severe protein denaturation (Longmore 1, Lee 1), but Kirsh (2) states that this form of damage is not significantly more in 'bubblers' than in comparable membrane oxygenators. Indeed the Rygg bag and other types of bubbles are possibly the most widely used forms of oxygenation in to-day's operating theatres. Proctor (1973) supports the view that the bubbler
is more than adequate for present requirements and this type certainly has the advantage of simplicity.

1.3.2. Film Oxygenators.

In film oxygenators a large blood surface is presented to an oxygen atmosphere. To be efficient some mixing of the blood must occur. This may be achieved by allowing the blood to flow over a screen by gravity or by rotating cylinders or discs which 'pick up' a film of blood as they rotate. Discs are the most efficient class of film oxygenator. Film oxygenators have a thick film, low efficiency and a large priming volume. The risks of air embolism, bacterial infection and blood trauma are considerable.

1.3.3. Liquid Liquid Oxygenators. (Wallace (2) 1973)

Gas bubbles are encapsulated within a thin film (<1μ) of inert fluorochemical preventing a blood gas interface. The gas bubbles are passed countercurrent to the blood. As the bubbles emerge from the gas phase, they collapse, releasing CO₂. The Fluorochemical is reusable and very high performance figures are claimed with no measureable alterations to proteins, formed elements or clotting factors attributable to the use of the fluorochemical.

1.3.4. Membrane Oxygenators.

In membrane oxygenators, the blood and gas phases are separated by a gas-permeable membrane in the form of thin sheet or tubing. If the membrane is tubular, the blood phase may be either internal or external. The advantages claimed for membrane oxygenators are low priming volume and minimised hemolysis and protein denaturation. Kayser,(1974), maintains that this superiority is not yet clinically proved.

1.4. Unique Applications of Membrane Oxygenators.

The benefits of membrane oxygenation may not be proved, but even if they were, what promise is there for the future? The applications foreseen for membrane lungs can be divided into four categories:-

1.4.1. The Replacement of Existing Oxygenators in Routine Surgery.

The anticipated reduction of blood damage in prolonged heart lung bypass could minimise sludging, associated emboli, post-operative trauma and possible death. 20 years of experience in the use of heart lung machines have proved gas contacting oxygenators adequate for most cardiac operations. However, if such operations require
more than, say, 2 hours, unforeseeable complications may arise
(Gerbode 1967).

To persuade surgeons to replace their existing oxygenators, the
membrane oxygenator must be economical, reliable, easy to use and
cause fewer complications and hence improve patient survival.
Although the cost of using membrane oxygenators has fallen in recent
years, they will probably never be competitive at this level. It
will be the lowered complication rate which will lead to the eventual
adoption of membrane oxygenation, if anything.

1.4.2 The Provision of Long Term Support.

With minimal blood trauma being caused the patient may be able to
deal with what little damage is caused and the time constraint on
bypass may be removed. The provision of extracorporeal support
lasting days or possibly weeks in cases of acute but potentially
reversible respiratory or cardiac failure might allow time to recover
sufficiently to permit definitive treatment (Drinker 1972).
Respiratory failure is routinely treated with artificial ventilators.
These have their limitations, especially when the cause of the
distress is at the alveolar membrane level as in hyaline membrane

Drinker (1972) suggests two examples where extended bypass would
not be expected in itself to produce significant or permanent
improvement, but might allow the recovery time for treatment to be
applied. The first is veno-arterial bypass in cases of cardiogenic
shock prior to and during myocardial revascularization, and the second,
extracorporeal support of patients with cystic fibrosis who, during
acute crises, could be helped by pulmonary lavage. It has also been
suggested that extracorporeal support following pneumonia (Spenny 1973)
aspiration pneumonitis and in cases of wet lung syndrome might be
possible using an improved membrane oxygenator system.

Hill and Zapol are among the leaders in this field.

1.4.3 Pediatric Surgery.

Gas contacting devices have proved so unsuccessful that open-heart
surgery on new-born infants is not undertaken. Palliative measures
without bypass are favoured. Membrane oxygenators, however, have
Deep hypothermia with circulatory arrest (Dillard 1963) has been applied successfully to formerly untreatable conditions.

Such operations are still time limited and best carried out in older infants. Wright (1973), with the experience of many successful infant operations using the Landé-Edwards membrane oxygenator, claims that the ease of the operation, compactness and low priming volume gives special promise for pediatric surgery.

1.4.4. The Storage and Transplant of Organs.

In storage, proteins must not be denatured since there are no mop up systems. A membrane oxygenator system of organ perfusion has been suggested (Brown 1971) and for temporary support in lung transplantation operations (Corso 1973).

1.4.5. Summary.

It has been suggested that in pediatric surgery and cases where long-term bypass for palliative treatment can allow time to recover for an appropriate operation, the benefits of membrane oxygenation might be utilised. It might also replace bubblers in longer routine cardiac operations like valve replacement, support organs prior to transplant and even allow the lung to be collapsed during cardiac operations to allow the surgeon more room. The greatest immediate promise would appear to be in the treatment of neonatal respiratory distress.

1.5. Historical Review of Progress in Membrane Oxygenation.

The history of membrane oxygenation goes back only 30 years; early progress was slow since the membrane materials first chosen were of very low permeability.

Since the production of silicone rubber in thin sheets progress has been dramatic and commercially viable membrane oxygenators are now available. Below is a summary of the major landmarks in the development of the membrane lung.

1944. Gas exchange through synthetic membranes was observed by Koff (1944) in his kidney machine.

Late '40s Silicones were introduced.

1955 The first true membrane oxygenator, a capillary type using polyethylene tubing was described. It was used for animal perfusions. (Clowes(2) 1956). Clowes confirmed that Ethyl Cellulose and Polyethylene were the most suitable membrane materials available to date. (Clowes (1, 3) 1956).
1957 Kamermeyer reported the high permeability of Dimethyl Silicone Elastomer, forty times that of Teflon.

1958 Clowes reported that Teflon had improved permeability over Polyethylene, but the cost and fragility of Teflon persuaded him to continue using Polyethylene. Thomas dipped nylon mesh in Silicone rubber to produce the first Silicone membrane.

1962 Marx applied Thomas's technique to make an experimental membrane oxygenator.

1963 Bodell produced the first Silicone capillary membrane oxygenator.

Mid 60s Several companies were producing silicone film for oxygenators by dip coating, batch casting and later calendering. The development of extrusion processes led to the manufacture of thin walled tubes. Teflon, however, was still the widest used material.

1965 The first practical membrane system was produced - the Bramson lung.

1967 Illickal showed that membrane limited transfer could be achieved by a disc spinning technique.

1969 Burns produced ultra thin silicone rubber film. The Landé-Edwards oxygenator was produced. Drinker used an oscillating toroidal capillary membrane oxygenator to improve performance.

1971 The oscillating torus system was producing performances of 250 ml/m²min, 8-10 times better than the average static oxygenator.

Research has mushroomed since Burns discovery in 1969, workers are studying the traumatic effects of oxygenators, improving performance by better designs, or carrying out clinical work to gain practical knowledge.
1.6 The Advent of Silicone.

The ability to produce silicone rubber tubing and sheet gave designers an opportunity to produce working machines capable of supporting the at-rest requirements of the body. Dramatic progress was made and performance of these machines steadily improved as illustrated by the table below:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Membrane material</th>
<th>Thickness ( \mu )</th>
<th>Blood Vol. Ml/m²</th>
<th>Agitation</th>
<th>Area m²</th>
<th>Performance Oxygen cc/m²/fm</th>
<th>Blood Flow ml/m² min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clowes 1956</td>
<td>Teflon</td>
<td>12</td>
<td>130</td>
<td>-</td>
<td>0.5</td>
<td>22</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2 Peirce 1966</td>
<td>&quot;</td>
<td>12</td>
<td>140</td>
<td>-</td>
<td>0.13</td>
<td>50</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>3 Crescenzi 1963</td>
<td>&quot;</td>
<td>6</td>
<td>-</td>
<td>Gas pulse</td>
<td>0.62</td>
<td>-</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>4 Kystra 1961</td>
<td>Supported Silicone</td>
<td>3</td>
<td>180</td>
<td>Cascade</td>
<td>0.37</td>
<td>69</td>
<td>700</td>
<td></td>
</tr>
<tr>
<td>5 Bramson 1966</td>
<td>&quot; Silicone</td>
<td>250</td>
<td>180</td>
<td>Insert</td>
<td>5.6</td>
<td>35</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>6 Marx 1962</td>
<td>&quot; Silicone</td>
<td>125</td>
<td>340</td>
<td>&quot;</td>
<td>0.32</td>
<td>63</td>
<td>1800</td>
<td></td>
</tr>
<tr>
<td>7 Bodell 1965</td>
<td>Silicone</td>
<td>163</td>
<td>250</td>
<td>Blood pulse</td>
<td>0.1</td>
<td>83</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>8 Day 1964</td>
<td>Supported Silicone</td>
<td>50</td>
<td>250</td>
<td>Rocking</td>
<td>0.63</td>
<td>100</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>9 Kolobow 1963</td>
<td>&quot; Silicone</td>
<td>100</td>
<td>90</td>
<td>Gas pulse</td>
<td>1.2</td>
<td>100</td>
<td>1100</td>
<td></td>
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<tr>
<td>10 Landé 1970</td>
<td>Silicone</td>
<td>100</td>
<td>200</td>
<td>no</td>
<td>1.3</td>
<td>36</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>11 Peirce 1968</td>
<td>Silicone/Polycarbonate</td>
<td>50</td>
<td>250</td>
<td>no</td>
<td>1.2</td>
<td>60</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>12 Melrose 1971</td>
<td>Silicone</td>
<td>75</td>
<td>600</td>
<td>yes</td>
<td>0.56</td>
<td>130</td>
<td>400</td>
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\( x \) High performance figure using membrane only 0.003 mm thick.

\( y \) Low " " " " " 0.25 mm thick.

\( z \) " " " " " 0.1 mm thick and no attempt to agitate the boundary layer.

Progress became even more marked when Burns (1969) discovered a mass production process to produce silicone rubber sheet well under 0.04 mm thick. The requirements of a membrane material are that it should have high diffusion coefficients for oxygen and carbon dioxide, not be traumatic to blood, be available in thin sheets, be robust and handleable be free from pinholes and be cheap for disposability. Burns was able
to increase the tensile strength and tear resistance up to four times. Nevertheless, silicone rubber sheet develops a high static charge and is tacky, making it difficult to handle.

Currently, in membrane 25 - 50 μ thick, the pore size is between 4 - 8 x 10^10 m making a pore 30,000 - 125,000 times as long as it is wide - like a railway tunnel 60 - 240 miles long! It may still not be the ideal material, but as shown by the chart below, it is the best so far and all current work centred round it.

![Diagram of membrane materials](chart)

1.7. Current Work.

The only common factor in current research is the use of silicone rubber as the membrane material. The work on design and development of oxygenators can be classified under two major headings, tubular membrane oxygenators and flat bed (sheet) membrane oxygenators.

Of the former category, there are at least twenty static capillary membrane lungs undergoing trials, including those of Buckley (1969), Dorson (1969), Zings (1970), Bartlett (1972), Clevert (1973) and Kolobow (6). Notable among those perfecting the technique of oxygenating blood using a coiled tube is Melrose (1). By rapid oscillation of the coil about its axis, he has produced a greatly improved performance figure with minimal increase in blood damage.

Of the static, flat-bed membrane oxygenators in use, the Landé-Edwards (Landé refs (1-19)) and the General Electric-Peirce (Peirce refs. (2-15)) are in everyday use in routine surgery. These and others have been used in prolonged bypass by Hill refs (1-10), Carlson (5) 1972), Awad (1) (2) (4) and others, usually in the treatment of respiratory distress or insufficiency. Little attempt has been made
to improve this type of oxygenator by vibration, though some ingenious ideas have been suggested and used in their design. Claff (1967) introduced pulses to both gas and blood phases giving a similar effect to Longmore's pump-oxygenator (Longmore (1)). Palmer (1970) used a rocking oxygenator.

In addition to research on design, and possibly in the long run more important, work continues to improve the biocompatibility of oxygenator materials (Chang T, 1973, Galletti (5) 1970, Grode (1,2) 1969 et al.) and to produce more efficient membrane materials (Eiseman 1972). Others are studying the factors causing hemolysis (Blacksheer 1972, Bernstein 1971, Castenada 1969, Chang H,‡1972 et al.) thrombosis (Salzman (1-5), Stormorken 1971), and protein denaturation in extracorporeal circuitry. Finally detailed studies in hemodynamics may alter the design criteria of future membrane oxygenators.
CHAPTER 2.

2.1 Requirements of a Membrane Oxygenator.

A membrane oxygenator must be able to perform its task of gas exchange with a minimum of blood trauma. A more detailed breakdown of the physiological, hemodynamic and general requirements is given below.

2.1.1 Physiological Requirements.

The 'at rest' requirements of the body must be met:

1. 250 cc/min. of oxygen and 200 cc/min. of carbon dioxide must be exchanged (Galletti and Brecher - HL Bypass). Preferably the machine should be capable of exceeding these levels and of achieving performance figures (Galletti (11) 1972) in excess of 30 cc/mlm\(^2\)min.

2. 5 l/min. of blood must be returned against 180 mm Hg pressure (Lowe)

3. The partial pressure of oxygen (PO\(_2\)) in the arterial blood must be restored to 100 mm Hg (95 - 100% saturated) while that of carbon dioxide, PCO\(_2\), must be constantly restored to about 40 mmHg (Fig.p.94). CO\(_2\) retention causes respiratory acidosis while CO\(_2\) depletion causes respiratory alkalosis (Davenport 1969).

4. The pH of the blood must be held constant. This implies that the gas input to the oxygenator should be a carefully controlled mixture, e.g., 94% oxygen, 6% carbon dioxide (Chapman 1970).

5. The system must allow changes of temperature between 30 and 38°C, but not expose blood to more than 40°C (Longmore 1969).

6. Little blood trauma should occur.

7. Patient survival must be improved and the complication rate must be lowered compared to currently used oxygenators.

8. Antithrombogenic biocompatible materials must be used and as few as possible different materials.

9. Some form of clotting inhibition must be allowed for.
10. The priming volume must be low to minimise the risk of infection and immune reaction. If this volume were less than 1 litre, it would be possible to prime the circuit with plasma-like fluids without diluting the patient's blood too much. Volumes over 1.5 litres must be primed with bottled blood with inherent risks of infection, especially of jaundice and of sensitization to serum proteins and to minor blood groups. Ideally the priming volume of a bypass circuit should not exceed 0.5 litres so that sterile fluid or even the patient's own blood can be used. Patients with rare blood groups would require minimal quantities of transfusion blood from the blood banks.

2.1.2. Hemodynamic Requirements.

1. The pressure drop through the system should be as low as possible. Subatmospheric pressures should be avoided as far as possible.
2. The membrane should have the smallest area which fulfils 2.1.1-1.
3. The hydraulic geometry should be as simple as possible with a uniform area of flow and no sudden changes.
4. There should be no sudden decompression, snap-shut valves, turbulence, taps, sharp bends, nozzles or cannulae.
5. Ideally the circuit should be closed so that no level control is necessary.
6. For oxygen transport the limiting factor is the blood film, but for CO₂ transport, the membrane properties impose the limit.
7. The internal flow velocities should be low.
8. All surfaces should be smooth with no dead spaces.
9. If the circuit leaks it should leak outwards.

2.1.3. General Requirements.

A well-designed oxygenator should have the following characteristics:-
1. Higher efficiency than existing oxygenators.
2. Reliability.
3. Safety as a major priority. Twin systems, fail safe devices and warning systems should be included. There should also be an alternative power source to mains.
4. Simple construction with ease of dismantling and assembly.
5. The oxygenator and its associated equipment should be disposable or sterilizable. The latter process must not affect components.
6. Robust and compact construction.
7. Reliable instrumentation especially of flow rates. The operator must be able to control flow and pressure to suit different patients and to cope with the changes in demand during the operation.
   Ideally closed loop control of gas tensions in the blood should be employed.
8. The oxygenator should be inexpensive and easy to use.

2.1.4 Summary.

The above requirements are ably summarized by Longmore's ideal machine (1969) "A little box mounted over the patient's stomach with two knobs, one for flow, one for temperature, operated by the surgeon or his assistant. It should be so gentle that no haste is required by the surgeon and that no large team is required to operate it."

2.2 Design Considerations.

2.2.1 The Membrane.

The interposition of a membrane between the blood and gas phases 'solves' the problems alleged to be caused by the raw blood gas interface of other types of oxygenator, but creates two new ones - the membrane itself provides a resistance to gas flow and its presence also causes a slow moving boundary layer to be set up.

The membrane can be made thinner to reduce the resistance, but Abel (1) claims this is not a key factor in oxygenation and that increasing membrane thickness fourfold only reduces diffusion by 10%. Membrane thickness does become an important factor, though, in carbon dioxide elimination. With efficient mixing carbon dioxide transfer becomes severely limited by membrane resistance and with the oxygenator working at the membrane limit can only reach half the oxygen uptake rate.

The introduction of the membrane to the blood phase causes skin friction and sets up a relatively stagnant boundary layer or zone which inhibits gas transfer by impeding the progress of the blood. This problem, unique to the membrane oxygenator, is illustrated overleaf.
The stagnant layer receives the oxygen while the faster streams pass through the oxygenator having received a minimal quota of oxygen. A more detailed discussion is presented in Section 2.2.3.

Silicone membrane does present other problems associated with its physical and chemical structure. It is a tacky material which makes handling and assembly difficult. One suggestion was to powder with sodium bicarbonate to ease the problem. The surface texture shows ridge-like protrusions under the electron micrograph which can produce eddies and therefore mixing, but Zingg (2) claims that these may form bubbles at the membrane surface by entrainment.

Strengthwise, silicone rubber has a low tear resistance which gives a second reason for extreme care in handling. Thomas, Marx and Kolobow (2) and others prefer to reinforce the membrane in woven mesh to reduce the risk to patients at the expense of diffusion efficiency.

The diffusion of gases through the membrane increases with temperature and more importantly reduces on cooling, since many operations are carried out using a blood temperature of as low as 30°C. This effect is reduced, however, by the fact that increased temperature decreases oxygen fixation by the blood (dissociation curve moves to the right - see fig).
This suggests that oxygen should not be preheated, but that a heat exchanger be employed to maintain extracorporeal blood temperature.

Simiril and Herschberger found that membrane water content increased gas transfer, Benevenuto (1952) however, claimed the opposite. Other ideas for improving transfer are by:

a) Developing thinner membranes of adequate strength.
b) Exploiting the use of yet more permeable materials.
c) Pressurising the gas phase to increase the oxygen pressure gradient (Dagher 1959) or cycling gas pressure (Claff 1967).
d) Temporarily but reversibly altering the chemistry of the blood to improve the rate of transfer through the plasma or across the red cell wall, possibly at the cost of cell fragility.
e) Improving flow characteristics.
f) Treating the membrane in some way to improve its permeability.

Hydrogen Peroxide has been suggested as a catalyst to gas transfer.

Most workers tend to reject the idea of pressurising the gas phase. While striving to manufacture yet thinner membrane, they see the increased dangers of air embolism following pinholes and tearing. It is thought essential that blood should leak out rather than air in, in the event of a flaw. The implication is that oxygenation pressure should be lower than blood pressure for safety, preferably marginally subatmospheric.

Some requirements for efficient gas transfer are impossible to achieve simultaneously. The time needed to oxygenate a film of blood, for example, varies as the square of the film thickness, implying large passages are inefficient, however, mixing by passive or active means is not really possible in narrow channels. The greater the blood transit time, the greater is the oxygenation efficiency (Benevenuto) but to maintain a given flow rate, the area of the membrane would have to be proportionately large.

Benevenuto concludes that the best oxygenation occurs with higher oxygen temperature and pressure, lower oxygen humidity and the thinnest possible membrane.
2.2.2 Capillary or Sheet?

Silicone rubber is more difficult to make into thin tube than sheet of the same thickness. The smallest diameter of tube currently produced is 100 μ, making precise mimicking of the alveolar capillaries impossible.

The difficulties with plate design oxygenators like the Bramson, Landé-Edwards, General Electric-Peirce lie in the control of the blood film thickness and in the production of uniform planar flow. Unmodified, the blood tends to form thick rivulets. Both these difficulties can largely be overcome by the addition of some design of 'blood screen' usually grooved as in the Landé-Edwards and GE-Peirce or meshed as in the Bramson lung. The interposition of the screen in turn increases the pressure drop and reduces both the blood flow and the effective membrane area. The manifolding necessary in both plate and capillary oxygenators, though more particularly in the latter, can cause thrombus formation, due to reduced velocity.

The advantages of capillary membrane construction lie in the easier control of flow, the lack of obstructions to flow and in the naturally occurring secondary flows or Taylor vortices. The capillaries do not then need to be of small diameter because of this mixing effect. The major disadvantage of capillary design is the higher cost per unit area compared to that of sheet, a prime consideration since the membrane must be disposable.

2.2.3 Hemodynamics.

The boundary layer problem, touched on in 2.2.1, would exist whatever liquid passed through the oxygenator, but the presence of discoid, red cells in the blood considerably complicates the flow pattern:-

```
THE SIGMA EFFECT
```
Depending on the size of channel, the wall material and the flow velocity, an axial core of oriented erythrocytes, together with a relatively cell free plasmatic zone is established - the sigma effect. The annulus has an immobile portion near the wall surface, where the stream is sluggish and cells tend to tether and shear (Blacksheer (1-6) (8), and has an inner mixing and shearing part. As flow is increased cells in the core tend to orient to present the least resistance to flow and rouleaux break up. Both the tethered cells and the plasma zone inhibit gas transfer. Active or passive mixing should alleviate both problems, shaking the tethered cells free or preventing tethering and causing an exchange of cells between the core and the annulus. What will never be possible is the mimicry of the lung where cells are presented singly to the alveolar membrane.

Since membrane oxygenators were first conceived mixing has been a feature of many of the designs:

<table>
<thead>
<tr>
<th>General Type</th>
<th>Special Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandwich</td>
<td>Screen in blood phase (Landé-Edwards)</td>
</tr>
<tr>
<td></td>
<td>Pneumatic or Hydraulic shim (GL-Peirce)</td>
</tr>
<tr>
<td></td>
<td>Multipoint support (Abel(1), Claff)</td>
</tr>
<tr>
<td></td>
<td>Recirculation</td>
</tr>
<tr>
<td></td>
<td>Oscillating gas pressure Pattern on membrane.</td>
</tr>
<tr>
<td>Coil</td>
<td>Oscillating gas pressure</td>
</tr>
<tr>
<td>Capillary</td>
<td>Pulsatility</td>
</tr>
<tr>
<td>a) Blood inside</td>
<td>Interweaving</td>
</tr>
<tr>
<td>b) Blood outside</td>
<td>Pulsatility</td>
</tr>
<tr>
<td>Envelope</td>
<td>Rhythmic tilting</td>
</tr>
<tr>
<td></td>
<td>Vertical cascades.</td>
</tr>
<tr>
<td>General Type</td>
<td>Special Feature</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Spinning Hollow Silicone Disc</td>
<td>Rapid rotation in blood (Illickal)</td>
</tr>
<tr>
<td>Toroidal</td>
<td>Taylor vortices</td>
</tr>
<tr>
<td></td>
<td>Rapid oscillation</td>
</tr>
<tr>
<td></td>
<td>(Melrose)</td>
</tr>
</tbody>
</table>

For efficient gas transfer with minimal blood trauma, convection and diffusion are required. Since diffusion is a function of concentration gradients and the properties of the conveying and diffusing substances, the best chance for gas transfer improvement lies in the convection process. As previously stated, this requires relatively large channels.

Illickal (1967) showed the membrane limit could be passed and that a near-linear increase in oxygenation with speed of active mixing could be achieved. Melrose (1972) has since discovered that oscillating a toroidal capillary membrane oxygenator, intensifying the reversed secondary flow, is nearly as good. He further showed that high energy mixing velocities of 100 - 200 cm/s, comparable to those found in the arterial system, do not seriously increase blood trauma and suggested that anticoagulents may not be needed at such flow velocities. Certainly, the problems of deposition and thrombi caused by flow being too slow must be minimal.

Only now are the benefits of creating lateral mixing by remixing, screens, curved passages, pulsation or agitation being fully explored. It is realised that the rise in efficiency promised could reduce the required membrane area by up to 80% and therefore make the oxygenator cheaper, simpler, more reliable and less damaging to blood ultimately.

2.2.4 Biocompatibility.

Materials found to be least traumatic to blood have in common a high degree of chemical inertia (Lowe 1969), smoothness of surface (Stewart and Surridge) and unwettability. These qualities are to some extent interrelated. Present trends of research into blood compatible materials divide into the following categories (Chang T 1973)

a) Surfaces with anionic radicals.

b) Surfaces of inert materials
c) Heparinised surfaces.

d) Albuminised surfaces.

To date the most extensively used construction materials for extracorporeal circuitry are:-

a) Stainless Steel.
b) Glass - preferably siliconised.
c) Silastic
d) Teflon
e) Some plastics.

Most common metals, other than stainless steel, tend to be toxic.

2.2.5 Physiological Considerations.

The dangers of low flow rates causing thrombi have already been mentioned. These cause emboli and greatly reduce membrane area. Simpler hydraulic geometry and smaller basic membrane area reduce hemostasis and thrombosis.

The possibility of air embolism may be minimised by supplying the membrane oxygenator with a total gas pressure below that of the blood, so that in the event of a perforation, blood leaks out, not air in. It is claimed that even in these circumstances air bubbles may be entrained at the membrane wall.

The major advantage claimed for the membrane oxygenator is that the absence of a raw blood-gas interface minimises blood trauma. The air interface should be avoided at all times even when filling the circuit (Stewart, Mddx.Hosp.) The trauma most likely to be caused, hemolysis and protein denaturation, are discussed fully in section 3.1.

Platelet counts decrease during perfusion and their function can be impaired to the point where hemostasis fails. This loss is not surprising since they perform by adhering to any rough surface and then burst to release repair-promoting chemicals. They tend to stick to all artificial surfaces (which are much rougher than any blood vessel) but their adhesiveness can be controlled with dextrans, aspirin and antihistamines.

Finally evidence exists of greatly reduced phagocytic activity following perfusion. Sepsis is an ever-present threat and the body’s normal immunologic defences are impaired. Albuminisation may well help to alleviate some of the harmful effects to the formed elements of the blood by artificial circulation.
2.2.6 Summary.

Most membrane oxygenators produce performance figures of 30 - 40 cc/mm m²/min. and are less than 20% efficient. Increased efficiency could quarter the required membrane area and lead to a cheaper, simpler, safer and more reliable machine. Thinner membrane increases efficiency but also the likelihood of pinholes, tears and handling difficulties.

2.3. In Vitro versus in Vivo Testing.

Basic performance data for membrane devices are best obtained in vitro where accurate control of blood flow, gas flow, temperature etc. is possible. Data may be obtained over a wider range and under steadier conditions than is possible with an ex vivo perfusion. Painstaking tests will glean reliable information on gas exchange, perfusion pressure and blood volume which will not be augmented by in vivo tests.

One important aspect of such in vitro tests is the examination of the effects of modifications to the design and of sudden changes in the important parameters of blood flow and gas flow. The advantages and problems are compared in the table below (Salzman 1971).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro</strong></td>
<td></td>
</tr>
<tr>
<td>Best standardised</td>
<td>Artefacts easily occur</td>
</tr>
<tr>
<td>Easiest to study in detail</td>
<td>May not be relevant</td>
</tr>
<tr>
<td><strong>Ex Vivo</strong></td>
<td></td>
</tr>
<tr>
<td>Subject-device iteration</td>
<td>Tends to be sensitive</td>
</tr>
<tr>
<td></td>
<td>Time limitations</td>
</tr>
<tr>
<td></td>
<td>Subject interaction</td>
</tr>
<tr>
<td></td>
<td>Conditions tend to change with time</td>
</tr>
<tr>
<td></td>
<td>Activation of substances.</td>
</tr>
<tr>
<td></td>
<td>Exhaustion of substances.</td>
</tr>
<tr>
<td></td>
<td>Range of testing limited.</td>
</tr>
</tbody>
</table>
Advantages & Problems.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vivo</td>
<td>Large experimental errors</td>
</tr>
<tr>
<td></td>
<td>Discontinuous observations.</td>
</tr>
<tr>
<td>Subject-device interaction</td>
<td>Few data points.</td>
</tr>
<tr>
<td></td>
<td>Expensive.</td>
</tr>
<tr>
<td></td>
<td>Difficult to study transients.</td>
</tr>
</tbody>
</table>

In vitro tests should be carried out using human blood. Substitutes such as animal blood, water/glycerol mixture or even water will never produce results which are clinically useful; at best they will merely be interesting. Ideally the blood should be fresh, heparinised and human.

The superiority of the membrane oxygenator is not yet proved (Kayser 1974). Superiority, if it exists, should be measured by reduced blood trauma, increased performance or both. Unfortunately the interposition of a membrane between the blood and gas phases renders the second of these parameters unlikely to be achievable size for size. Membrane oxygenators are likely to be more expensive and more complicated in construction, so they must compete on a minimization of blood damage platform. They must also attempt to compensate for the handicap of membrane resistance and boundary layer establishment by being highly efficient.

As suggested in section 1.4, the membrane oxygenator is already making possible new life-saving operations and holds even greater promise for the future. Clearly, the objectives of minimizing blood trauma and improving efficiency are worth exploring.

Current progress has no set direction. Rarely are the two objectives explored together. Kayser (1974) sets out a detailed criticism of current work and the conclusions drawn from it.

The objectives of this thesis are twofold:

2.4.1 Blood Damage Investigation - Aims.
2.4.1.1 To produce definite design criteria for the membrane oxygenator taking into account blood damage and oxygenation considerations.
2.4.2 To prove or disprove the superiority of membrane oxygenation over gas-contact type oxygenation in respect of protein denaturation.

2.4.1.3 To relate the hemodynamics and biocompatibility of a bypass circuit to their effect on blood.

2.4.2 Oxygenation Efficiency Improvement - Aims.

To determine the effect on oxygenation ability of:-

a) Gas pressure.
b) Gas composition.
c) Vibration frequency.
d) Time from commencement of test.
e) Blood film thickness
f) Membrane thickness.

2.5 Programme of Work.

The chronological order of work to be carried out in an attempt to achieve the objectives of 2.4 is shown below:-

1. Manufacture of oxygenator and of other circuit components not commercially or easily available.

2. Organisation of remaining circuit components, gas and blood supplies and anticoagulents.


4. Proof that sampling of blood is non time dependent - otherwise calibration.

5. Conduction of tests with 'analogous fluid'.


7. Choice of instrumentation and measurement techniques.

8. Development of computer program to convert PO\textsuperscript{2} to SO\textsubscript{2} taking pH and temperature factors into account.

9. Determination of hemolysis and/or protein denaturation attributable to each separate component in order to isolate that due to the membrane oxygenator.

10. Reselection of equipment and repeat of above if necessary

11. Performance of experiments to show how oxygenation and blood damage vary with gas pressure, gas composition, time from commencement of test, membrane thickness and blood film thickness.

12. Examination of the membrane before and after tests under electron microscope for signs of membrane damage and clogging.
13. Examination of blood samples to study oxygenation and cell damage.
14. Examination of techniques to eliminate clogging if proved to exist, or improve oxygenation by breaking up of boundary layer by vibration (low frequency to ultrasonic), static charge, chemical additives or blood screens.
15. Examination of the effect of these techniques on the blood and the membrane.
16. Production of flow visualization pattern for the membrane oxygenator.
17. Review and redesign of oxygenator where necessary.
18. Production of figures for the performance of the membrane oxygenator.
19. Relation of (18) to theory.
CHAPTER 3.

SELECTION OF EXPERIMENTS.

3.0 Introduction.

This chapter covers selection of instrumentation and measurement techniques and the design of circuit components, items 1, 2 and 7 in the programme of work on page 31.

The possible methods of measuring each parameter are listed and a choice made based on current literature, available equipment, ease of use and relevance.

The chapter ends with the selection of specific experiments to achieve the aims listed in section 2.4.

3.1 Selection of Tests to measure Performance and Blood Damage.

3.1.1 Measurement of Oxygenation Performance.

No standard has been agreed which would allow the many different oxygenators in current use to be compared. Galletti((7) 1971) suggested a 'rated flow' method, being the flow rate at which blood with a packed cell volume of 40% enters the device 65% saturated and leaves 95% saturated. The performance of an oxygenator or its 'rated oxygen transfer' in ml/m²/Min. at the 'rated flow' could then be quoted.

The difficulty lies in the maintenance of the parameters quoted at their calibrating levels long enough to record the necessary data to calculate gas flow. Certainly, though, it is necessary to measure the arterial and venous partial pressures of oxygen and carbon dioxide together with the flow rate. It is also necessary to maintain a record of blood pH and temperature.

Knowledge of the dissociation curve (J App Phys 21:3,1966) or a nomogram (Aberman 1973), equation or analogue produced from it will allow the percent saturation difference between the arterial and venous lines to be calculated. This can be achieved more rapidly, less accurately, but by continuous monitoring using one of several types of oximeter. The principle of these lies in the colour differential between arterial and venous blood:
The spectra correspond at various isobestic points at which calibration is performed. The colour of the reflected or transmitted light is then used to give a measure of oxygen saturation.

The performance of the oxygenator is calculated from

\[
\text{Performance} = \frac{\text{Blood flow rate} \times (\text{Art} - \text{Ven}) \times \text{saturation}}{\text{membrane area}} \times \text{hemoglobin content}
\]

3.1.2. Blood Damage.

Berstein (1971) has stated that wall interaction is the most important cause of blood damage. Firstly a protein monolayer forms on the artificial surfaces (which may subsequently be denatured) followed by the adhesion of platelets, then of red and white cells. Finally fibrin is deposited and breaks down (Forstrom 1971).

The trauma caused may include hemolysis, protein denaturation, agglutination, emboli, sludging, platelet loss and phagocytic damage.

3.1.2.1. Hemolysis - Discussion.

Hemolysis, which is thought to be of mechanical origin, is evidenced by an increase in serum hemoglobin, a virtual absence of haptoglobin, a reduction in erythrocyte life span and the presence of fragmented cells in circulating blood. It is the process of lysis of the red cell membrane and the subsequent release of cell contents into the plasma.

Plasma hemoglobin increases the viscosity and osmotic pressure and therefore upsets the oxygen exchange. Normal physiological levels are 0.6 - 4 mg per 100 ml. Above 150 mg per 100 ml, hemoglobin
appears in urine and in Blackwater fever when the level rises to 1000 mg per 100 ml the urine is black but patients still survive. The reticulo-endothelial system can clear 13 mg per 100 ml per hour indefinitely in a healthy individual, but under bypass conditions, renal failure, in the presence of acidosis, shock, renal ischaemia and dehydration and death may result (Andersen 1966). Kidneys clear the blood stream but hypothermia and hypotension reduce their efficiency (Galletti & Brecher HLB - 266). Longmore (1968) holds an enquiry if hemolysis rises above 40 mg per 100 ml during an operation.

Hemolysis can be aggravated by several flow characteristics. Blood is intolerant to sudden decompression, for instance, when mechanical valves shut and when flow is turbulent. Yarborough (1966) states that rapid hemolysis occurs where Reynold's number exceeds 4200. Under these circumstances hemoglobin comes out with explosive violence to rupture red cells, hence for a given tube size, there is a critical flow rate which, if exceeded can cause hemolysis. Surface material (Hirose 1969), surface roughness (Longmore 1968), (Stewart & Sturridge 1959) and overheating also promote hemolysis, as do over or under occlusion of tubing or peristaltic (roller) pumps. (Bernstein 1967) A hostile pH level in the plasma promotes hemolysis and may cause grotesque distortion of the erythrocyte's biconcave disc shape. Precoating circuitry with albumen may reduce hemolysis and is standard practice for the Landé-Edwards Membrane Oxygenator. Most important of all, bubbles and cavitation must be avoided, implying that there should be no sudden enlargements in the circuitry (Galletti & Brecher).

Blood is generally more tolerant to positive pressures than to even very small subatmospheric pressures, viz., cardiotomy suction line (Mc Caughan 1958). Intermittent high pressures, though, are thought to be detrimental (Chevret & Besson 1958, Björk & Rodriguez 1959).

Blackshear (1-5), (8) relates hemolysis to cells interacting with an adjacent wall. This hemolysis depends on the wall area, the 'stickiness' of the wall material and the blood flow rate. He also describes two time dependent forms of damage unrelated to such interaction: a low level of shear stress (1000 dynes/cm²) applied for several seconds or a very high level (40,000 dynes/cm²) applied for less than 0.1 seconds. The second of these may occur in prosthetic valve recipients who have high blood pressure. Heart pumps (Castenada 1964, Bernstein 1967) and membrane and non-membrane oxygenators
(Peirce (14) 1969) have all been closely examined and compared for henolysis. There is, however, no agreement as to the method of hemolysis measurement, nor has the hemolysis been related to other forms of damage such as protein denaturation.

One final point is of relevance to this thesis: the dilution of blood with physiological solutions such as saline or ACD decrease the liability of erythrocyte destruction.

3.1.2.2 Methods of Hemolysis Assay.

Most of the methods suggested for hemolysis measurement determine the quantity of hemoglobin released into the plasma. Some of these techniques are listed below:

1. Wu's method. (Wu 1923)
2. Benzidene Method.
3. Orthotolidene method.
4. Modified Benzidene method (Crosby & Firth 1956)
5. Cripps method (Cripps 1968)
6. Cyanmethemoglobin method (Fleisch 1960)
8. Radioactive tagging (Blackshear (5))
10. Measurement of Endogenous Production of Carbon Monoxide (Wallace (1) 1969)

In all cases, it is essential to eliminate whole red cells from plasma since they contain 13-18g per 100 ml.

3.1.2.3 Selection of hemolysis Methods.

Methods 3, 5, 6 and 7 were selected for further study. The Benzidene methods (2,4) were eliminated on health grounds as benzidene is a carcinogenic material. Methods 8, 9 and 10 have not been generally accepted in the field of artificial lung research.

3.1.2.4 The Orthotolidene Method.

Plasma is separated, by centrifuging at 5000 rev/min. for 15 minutes, drawn off and refrigerated until needed for measurement.

1 ml of a known solution of ortho-tolidene is added to 0.02 ml of plasma. 1 ml of hydrogen peroxide is then added, which starts a peroxide reaction catalysed by hemoglobin. After exactly 10 minutes the resulting dark green solution is diluted with 10 ml of acetic acid slowing the reaction to a near standstill. An extinction co-efficient is then read without delay on the spectrophotometer.
A calibration curve is drawn on readings for various dilutions of whole lysed blood.

3.1.2.5. Cyanmethemoglobin Method.

0.02 ml of the plasma is diluted in 4 ml of Drabkin's solution made up from 'aculate' diluent pellets. Hemoglobin, methemoglobin and carboxyhemoglobin (but not sulphhemoglobin) are converted to cyanmethemoglobin in the ten minutes allowed for the solution to stand. The optical density (OD) of the solution at 540 nm is compared to that of a standard solution (BDH) and to a reagent blank (with an Ilford 625 filter). The plasma hemoglobin level in the sample is calculated by:

\[
\text{Hemoglobin (mg\%) } = \frac{\text{OD sample} \times \text{conc.std. (mg\%) \times dilution factor}}{\text{OD standard}}.
\]

Alternatively a standard curve is produced of Optical Density against Plasma Hemoglobin concentration by diluting the standard in with the reagent in increasing amounts and determining the optical density of each. The optical density of the specimen is then merely translated into a hemoglobin concentration from the curve.

3.1.2.6. Cripps Method.

A stock solution of oxyhemoglobin is made by hemolysing red cells of pooled heparinised blood with distilled water, the solution then being separated by centrifugation.

Suitable dilutions of this solution are made in phosphate buffer (pH 7.5) to obtain final concentrations of oxyhemoglobin in the range 5-150 mg\%. The hemoglobin content is found by making parallel dilutions in Drabkin's solution and comparing with a known cyanmethemoglobin standard as in the previous method.
The absorption of oxyhemoglobin is determined at 560 nm (x), 576 nm (y) and 592 nm (z) and the quantity 2y - (x + z) is calculated for each sample. The graph of oxyhemoglobin concentration in mg% against this quantity is linear.

An allowance can be made for errors introduced by the presence of bilirubin in the sample.

3.1.2.7. The Atomic Absorption Method.

The plasma sample is sucked into the injector pipe and vaporised.

The Atomic Adsorption Spectrophotometer.

The serum iron in the sample increases the atomic adsorption and reduces the light energy received at the detector. The adsorption is a linear function of iron in the sample and is compared with the adsorption of a commercially produced, freeze-dried serum standard. The method is capable of recording changes as low as 1 mg iron per 100 ml serum. Since 100 gm of hemoglobin contains 0.35 gm iron, the accuracy of the method should be ± 0.28 mg% plasma hemoglobin. Bilirubin which is not an iron derivative causes no problems.
3.1.2.9. Protein Denaturation - Discussion.

It has been claimed that denaturation results from the use of heart-lung machines, causing:

1. Mortality of several percent of patients, which rate increases with perfusion time.
2. Sludging.
3. 100% incidence of cerebral fat embolism.
4. Neurological complications in 6 - 20% of heart lung cases.

Factors which cause hemolysis could also cause denaturation, but one factor which is thought to be conclusively linked to denaturation is the blood gas interface (Anson (1945, Dobell (1965), Lee (1961), Wright (1962), Zapol (1972)).

Denaturation changes physical and physiologic properties and results in an unfolding of the protein molecule. The hydrogen bond in the main linkage is destroyed, the spatial arrangement of polypeptide chains is changed to a more disordered arrangement within the molecule. The proteins are subtly altered so they no longer function properly. Surface tension is changed, enzymatic activity is lowered and there is a loss of antigenicity. Boiled egg white is often quoted as an example of the effect of denaturing protein.

As well as the blood-gas interface, x-ray, and ultraviolet irradiation (Harper), heat (Lee 1971), pH changes, membranes with high dielectric constant; and contact with heavy metals, e.g., zinc, all cause denaturation. Denatured protein is less soluble, can be removed by filtration, and has a lowered biological activity. Under certain circumstances the process of denaturation may be reversible.

Denaturation increases plasma turbidity and viscosity and may affect the mobility of the protein in electrophoresis. Other methods which might be employed to detect the presence of denatured protein include gel filtration, ultracentrifugal, optical rotary dispersion, circular dichroism, hydrogen exchange viscosimetry, x-ray diffraction and nuclear magnetic resonance.

No agreement is reached on the effects of denaturation or on its quantification. Lee ((1) 1961) suggests that morbidity and mortality may be connected to denaturation by either 'sludging' or by alterations
in blood lipids. His analysis technique appears to be a visual inspection of the paper electropherogram and he claims an 8 - 10% increase in globins for non-membrane oxygenators and only 2 - 6% for the membrane oxygenator. In a more recent paper (Lee (3) 1971) he claims denaturation may also alter immune or host resistance mechanisms. Wright (1962), also highlights the possible relationship between denaturation and complications following prolonged bypass. His experiments comparing the effects of membrane and non-membrane oxygenators used the Spinco Analytrol to analyse paper electropherograms. He observed slight changes in the electrophoretic pattern and an increased mobility of the $\alpha_2$ globulin but thought these to be insignificant. Peirce ((10) 1973), however, based on the evidence of Dobell (1965), Zapol ((3) 1972) and others, is convinced that denaturation is less marked in the membrane Lung and in his ref.((9) 1973) requotes Lee's ((2) 1961) results.

In a recent paper, Kayser (1974) examines the work of Lee, Kauzmann, Anson and others working on the relationship between denaturation and the type of oxygenator used. He criticizes the lack of experiments conducted under physiological conditions and the irrelevance of many of the experiments performed to clinical application. He concludes that the mechanism of protein denaturation described in protein chemistry literature may not be relevant to modern oxygenators, that there are no proven significant differences between membrane and non-membrane oxygenators and that the use of membrane oxygenators on the assumption that they are more physiological is unjustified. He quotes Peirce((14) 1969) to confirm his views.

3.1.2.10 Methods of Protein Denaturation Assay. (Kauzmann)

The following tables list methods of detecting alterations to tertiary structure of proteins and to short range properties both of which are reckoned to occur in protein denaturation.

Table 1. Shape Properties

Hydrodynamic properties

A) Friction Ratio
B) Viscosity increment
C) Rotary diffusion constant (flow birefringence, dielectric relaxation, fluorescence depolarization).
Radiation scattering
A) Light scattering
B) Small angle x-ray scattering
Long-range electrostatic effects on titration curves, Linderstrøm - Lang's 'W'
Electron microscopy
Second virial coefficient of moderate salt concentrations
Surface properties
A) Force-area curves at moderate pressures
B) Surface dipole moment
C) Area of solid film.
Dipole moment
Diffusion through membranes with controlled pore sizes, Craig
3.1.2.11 Table 2 Short-range properties.
Thermodynamic Properties
A) Energy and Heat capacity
B) Entropy:
C) (Free energy)
D) Volume, compressibility and coefficient of expansion
E) Solubility, activity, distribution between solvents.
Optical Properties
A) Optical rotation and dispersion
B) Infra red absorption
C) Visible and ultraviolet absorption
D) Wide angle x-ray diffraction
E) Index of refraction (polarizability, anisotropy)
F) Depolarization of fluorescence (in some cases).
Chemical Properties
A) Reactivity
B) Intrinsic pH's of acidic and basic groups
C) Hydrogen - deuterium or hydrogen-tritium exchange.
D) Binding of small molecules, dyes, ions and the like.
E) Immunochemical properties
F) Digestibility by proteolytic enzymes
G) Biological activity
H) Electrophoresis (isoelectric point, zeta potential)
Nuclear and electronic magnetic resonance.
Surface phenomena
A) Spreadability
B) Surface viscosity
C) (Surface dipole moment)

3.1.2.12. Selection of protein Denaturation Assay

Of all the methods of assay listed none is better known than electrophoresis. With the limitation of available equipment and time constraints it was decided to adopt this method. However, within this category are a number of techniques:-

1. Paper electrophoresis at low voltage
2. High voltage paper electrophoresis
3. Thin layer electrophoresis
4. Cellulose acetate electrophoresis
5. Immuno-electrophoresis
6. Agar gel electrophoresis
7. Starch gel electrophoresis
8. Acrylamide gel disc electrophoresis

3.1.2.13 Selection of Electrophoretic Method.

Electrophoresis on cellulose acetate membrane is particularly suited to the study of serum proteins (Kohn) and the electropherogram produced is particularly convenient to analyse quantitatively. The method has the following advantages over paper electrophoresis.

1. Satisfactory separation can be achieved over a relatively short distance after a relatively short running time at low voltage.
2. Background staining is minimal and photoelectric scanning gives reliable quantitative results.
3. Cellulose acetate is soluble in some solvents (Acetone) making colorimetric estimation of the separated zones convenient and accurate.
4. Proteins being non adsorbed can be studied above and below their isoelectric points,
5. A better separation of α-globulin can be obtained.
6. Serum proteins stain particularly well and their dye uptake is very similar.
7. Very small samples can be studied (1 mg / 1 μl S)
8. Cellulose acetate membrane is virtually free of contaminants.
3.1.2.14 The Method of Acetate Electrophoresis

The acetate sheet is first soaked, right way up in \((8.6 \pm 0.1)\) buffer by resting it on the surface then submerging after five minutes. To a small smear of Bromo-Phenol Blue is added the serum on each segment of the applicator plate. The acetate sheet is removed and gently blotted and the applicator having been tested once or twice on blotting paper is touched lightly and evenly on the sheet at one inch from the 'black lead' end. The sheet is then placed square on the cloth electrode, the lid replaced and the current \((210 V)\) switched on for 20 minutes.

The strip is then removed and placed in 0.5% Ponceau Solution 7.5% TCA for six minutes and submerged. The strip is finally cleared in two or three rinses of 5% acetic acid.

3.1.2.15 Methods of Analysis of Electropherograms (Whitaker 1967)

If electrophoresis is carried out under strictly controlled conditions quantitative analysis may be achieved in any of the following ways:-

1. Visual comparison - The density of colour and the size of zone are compared visually with those of a known standard. Accuracy \(\pm 10 - 20\%\).

2. Area of zone (Fisher) - The areas of zone of known and unknown are determined following photographic enlargement and weighing. Accuracy \(\pm 5\%\)

3. Total colour density (Block 1, Bull, Redfield) - The electropherogram is scanned in a densitometer at the wavelength maximum of the detected zones. The baseline is determined by scanning blank strips. The absorbance versus the distance along the electropherogram is plotted manually or automatically. The area under the curve for each fraction is then determined automatically (e.g. using the Spinco Analytrol - Lee), by weighing or using a planimeter. These are again compared with standard concentrations. Accuracy \(\pm 5\%\).

4. Maximum Colour Density (Block 2) - As above, the trace is scanned in the densitometer but here the maximum colour density is compared to the standard. Accuracy \(\pm 5\%\).

5. Area X Absorbance Method - combines methods 2 and 4 but appears to offer no advantages over 4.

(Dent, Cousins, Dixon, Wilson).
6. Elution - The most accurate method but one requiring enormous care and precision

A wedge shaped strip is cut from the zone and by a variety of possible methods is soaked in the eluting fluid and the element is collected and applied to a second support. The concentration of the solute is then determined by the usual forms of analysis.

3.1.2.16 Selection of Method.

Of the six listed methods (1) was eliminated on the grounds of low accuracy, (2) because of the difficulties of using the method on a sample containing several fractions, (5) since it offered no advantages over (4) and (6) because of the high level of skill, precision and time involved.

Of the two remaining methods, 4 was considered to have the greater relevance to exploring the changes of the relative proportions of fractions in the sample.

The areas, as stated previously, can be found using a planimeter or by cutting out and weighing. The problem though, is to estimate areas at an overlap.

\[\text{Diagram showing areas at an overlap.}\]

This may be done in three ways.

1. Where the overlap is small, a perpendicular may be drawn between each 'trough' and the base line.

2. By isosceles triangles:
$AB$ is drawn from a peak down the 'remote side' of the curve from the trough. $CD$ is similarly drawn for the second peak. $AE$ and $CF$ complete isosceles triangles, $CDF$ and $AEB$. The shaded area is shared between left and right hand 'peaks'.

3. By analogue computer.

The first of these ways was selected for convenience. The method required the use of a densitometer whose settings are shown below.

The trace was produced by a pen recorder from the electrophorogram. One such trace is shown below.
3.1.2.17 Agglutination

The surface of the red cell carries protein agglutinogens which combine with 'foreign' agglutin to form protein attachments which irreversibly cement the red cells together in clumps. It occurs in a mismatch of blood groups and following pumping through an in-vitro circuit.

Measurement of the Erythrocyte Sedimentation Rate (ESR - normally 1-12 mm/hour), the rate at which red cells settle in plasma, gives an indication as to the extent of clumping. It depends on surface tension and surface area and therefore increases where rouleaux are formed in which case there is increased fibrinogen and globulin but reduced albumin. The rouleaux are harmless in themselves but promote thrombus formation, reducing oxygenator efficiency.

3.1.2.18 Emboli

Emboli may be thrombi, fat globules, tumour cells, ghost cells or even air bubbles. Poor hemodynamics especially low flow rates, promote thrombi as does the presence of positive electrical charges. They greatly reduce effective membrane area and are one of the major causes of death on the operating table. A visual observation of macro emboli will be undertaken.

3.2.19 Platelet loss and White cell loss.

Extra corporeal circulation is known to lower platelet count impairing function sometimes to the point where hemostasis fails. As with other particles, deposition of platelets is most likely to occur at stagnation points. In invito tests, white cell count falls dramatically. However, in vivo, the opposite happens as the body builds up defences in the presence of a large amount of foreign material. Although platelet and white cell counts are interesting they are not considered highly relevant to this thesis.

3.1.2.20 Sludging

Intravascular sludging is directly relatable to the in vitro ESR. It is the irregular massing of red blood cells and emboli and is the next stage following rouleaux formation. It can be aggravated by contact with high molecular weight dextran or gelatin. Sludging is a difficult parameter to quantify and a merely visual check on the extent of its presence will be noted.

A check will be made, however, on the effect of sludging on the membrane material using the scanning electron microscope. Samples of the membrane before and after use will be compared for signs of 'clogged' pores.
3.2. Choice of Instrumentation.

3.2.1. Oxygenation performance

The gas supplies from British Oxygen special gases are monitored for flow rate using GEC/Elliot rotameters and for pressure using simple glass (water or mercury) manometers.

The blood gas content is recorded by drawing samples slowly through a short section of silicone rubber tube in the circuit (which self seals) and with disposable needle and syringe. (Needle gauge as recommended in Dacey and Lewis). The sample is inserted in the Radiometer BMS 3 instrument and the PO\textsubscript{2}, PCO\textsubscript{2}, and pH automatically indicated on the Radiometer Digital Acid Base Analyser PHM 72c.

3.2.2. Blood condition measurement

The initial condition of the blood is noted by examination under the microscope for crenated or damaged cells and by a microhematocrit using a Gallen-Kamp Junior centrifuge and a Hawkesley reader to determine packed cell volume. The latter requires a modification to allow for the dilution of blood by ACD.

Hemolysis measurement is achieved as described using either the Pye Unicmic SP 600 Spectrophotometer or the Atomic Adsorption Spectrophotometer.

Electrophoresis measurement employs the Shandon electrophoretic tank and the Vitatron Densitometer and Recorder.

Red Cell counts, where executed used the modified Neubauer chamber.

3.3. The Construction of a Working Model Oxygenator

As stated in section 2.2.3 and 2.3, blood is a highly complex fluid which lends itself neither to analysis nor to analogy. The superiority of the membrane oxygenator is felt rather than proved, the relationship, if any exists, between hemolysis and protein denaturation has not been satisfactorily demonstrated nor have the effect and interdependence of all the relevant parameters of blood flow, gas flow etc. been studied simultaneously. The only way to usefully assess a membrane oxygenator is to build one and test it as near under physiological conditions as possible.

The only silicone rubber available was a very limited supply of 0.003 in thick sheet. This put design constraints on the model of both type and dimensions (see following drawings).
The main features of the design are:

a) Manufactured in perspex, relatively biocompatible and transparent so that the blood flow can be studied and leaks discovered easily.

b) Easily dismantled for cleaning, (chemically).

c) Facility to vibrate oxygenator linearly in any direction and to record the amplitude and frequency of the vibration.

e) Small priming volume so that only small quantities of blood need be used.

To test the gas transfer capabilities of the oxygenator the following components are also required:

a) Film deoxygenator
b) Peristaltic pump
c) Heat exchanger
d) Pipework and connectors.
e) Gas supplies and instrumentation
f) Bubble trap
g) Vibrator.

Items, a, f and g were also designed by the author for this series of experiments.

3.3.1 Constructional Details

The Oxygenator

Since the only form of silicone rubber readily available and suitable for use in an artificial lung was in 24 cm. wide sheet, the oxygenator was necessarily designed as a flat plate type. The scarcity of the material confined the dimensions to a small scale and rendered the possibility of a multistage oxygenator impracticable.

The oxygenator designed by author for testing purposes, consists of a sandwich of five perspex components (see figs. 1 - 6). The centre component, the blood screen, is shown in figure 3. It consists of a frame containing a drilled manifold of uniform section area each leading from the entry and exit nipples to a large central area which is designed to take an annealed glass fibre screen or to remain open.

The membrane sheets are mounted on either side of the blood screen and are retained and sealed by thin rubber gaskets. Thick gas frames are added to each side over the seals, the thickness aiding the spreading of the clamping forces and to increase the strength of the unit.
Finally the two covers are placed with further rubber seals to render the two gas chambers gas-tight. The chamber may take a metal support frame, a support sponge or a multipoint support.

The pressure in the blood phase is designed to be slightly higher than that of the gas phase so that bubbles will not arise in the blood should the membrane be perforated.

Blood is introduced from both sides of the inlet manifold and led from both sides of the outlet manifold. Gas may be introduced into both chambers simultaneously in either parallel or contraflow or alternatively flow from one chamber to the second in series.

The perspex covers enable the blood flow to be studied within the oxygenator if the metal support frame is used and thrombose, leaks and flow changes may be observed as they happen. The metal support screen however, severely reduced the effective area of the membrane by more than 50%. The alternatives are: to let gas pressure alone support the membrane in which case there is no control over blood flow; to use a multipoint support or to use a sponge support.

3.3.2 The vibrator.

The oxygenator was designed to be clamped in any attitude on the strip steel beam shown (fig.7) The beam may be forced to vibrate using one of a series of discs on an eccentric pivot driven by an electric motor at between 0 and 400 rev/mm. The amplitude of motion is controllable by altering the radius at which the link arm pivot is clamped. Alternatively a Ling-dynamics vibrator may be used being directly connected to the beam centre and driven by an oscillator. The control over the amplitude of motion is then lost but both frequency and amplitude are monitored by an end-mounted record player pick-up, the signal from which may be fed to a pen recorder.

3.3.3 The deoxygenator

The deoxygenator (fig.8) is a glass film-type manufactured in the University. It consists of a central vertical inlet tube which feeds blood to the top of an undulating cascade. At the base a reservoir collects the blood and this is drained off through the outlet tube. The cascade is situated in a glass gas chamber whose inlet is above the reservoir level and whose exit is at the top of the chamber. The oxygenator is highly efficient since it is the faster outside 'layers'
FIGURE 2

FILM OXYGENATOR
of blood that are presented to the gas. Control over the reservoir height is achieved by raising or lowering the whole oxygenator on its stand since the outflow is proportional to the head of the reservoir.

3.3.4 The Pump

A standard Watson-Marlow, 3-roller, peristaltic pump was used. This gave a pulsing flow up to a maximum rate of 100 ml/min. Silicone rubber tubing was used.

3.3.5 The Heat Exchanger

A small glass coil heat exchanger proved unsatisfactory. In its place a Gallenkamp reservoir plus heater, thermostat and stirrer unit provided the constancy of temperature. A large volume of water was used and evaporation from its surface was inhibited by a surface covering of small plastic capsules. The coil was suspended with the stirrer along its axis.

3.3.6 The Bubble Trap (fig. 9)

This was designed as an inverted U-tube with a central vertical tapping. The blood is slowed through the wider section and the bubbles separate out and collect in the tapping. The gas may be released by opening the cock.

3.4 Selection of Experiments

Five series of experiments were designed to achieve the aims listed in 2.4.

a) G Series - Hemolysis tests on circuitry
b) P - " " " pump
c) F - Performance and trauma tests on Filmer circuit
d) M - " " " " on Membrane Lung
e) E - " " " " " exploring changes of parameter.

These are detailed overleaf.
### G. Series experiments

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Blood</th>
<th>Components in Circuit</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 1</td>
<td>Bovine + EDTA</td>
<td>F P M H R T</td>
<td>MO damage</td>
</tr>
<tr>
<td>G 2</td>
<td></td>
<td>F P M H R T</td>
<td>Vibration damage</td>
</tr>
<tr>
<td>G 3</td>
<td></td>
<td>F P H R T</td>
<td>Circuit damage</td>
</tr>
<tr>
<td>G 4</td>
<td>Bovine + ACD</td>
<td>F P H R T</td>
<td>Circuit damage</td>
</tr>
<tr>
<td>G 5</td>
<td></td>
<td>F P H R V</td>
<td>Valve damage</td>
</tr>
<tr>
<td>G 6</td>
<td></td>
<td>F P H R T</td>
<td>Circuit damage</td>
</tr>
</tbody>
</table>

### P Series experiments

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Blood</th>
<th>Components in CCT</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 1</td>
<td>Bovine + ACD</td>
<td>R P R</td>
<td>Pump Damage</td>
</tr>
<tr>
<td>P 2</td>
<td>Human A + ACD</td>
<td>R P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 3</td>
<td>A + &quot;</td>
<td>R P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 4</td>
<td>O + &quot;</td>
<td>P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 5</td>
<td>A + &quot;</td>
<td>P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 6</td>
<td>A + &quot;</td>
<td>F P R</td>
<td>Pump + F Damage</td>
</tr>
<tr>
<td>P 7</td>
<td>A + &quot;</td>
<td>P R</td>
<td>Pump Damage</td>
</tr>
<tr>
<td>P 8</td>
<td>A + &quot;</td>
<td>P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 9</td>
<td>A + &quot;</td>
<td>P R</td>
<td>&quot;</td>
</tr>
<tr>
<td>P 10</td>
<td>A + &quot;</td>
<td>F P R</td>
<td>Pump + F Damage</td>
</tr>
<tr>
<td>P 11</td>
<td>B + &quot;</td>
<td>P R</td>
<td>Pump Damage</td>
</tr>
<tr>
<td>P 12</td>
<td>B + &quot;</td>
<td>F P R</td>
<td>Pump + F Damage</td>
</tr>
</tbody>
</table>

### F Series experiments

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Blood</th>
<th>Components in Circuit</th>
<th>Aims</th>
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</thead>
<tbody>
<tr>
<td>F1 - F18</td>
<td>Human + ACD</td>
<td>F: P: P: H R T B</td>
<td>Damage + Performance</td>
</tr>
</tbody>
</table>
M Series experiments

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Blood</th>
<th>Components in circuit</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1-M23</td>
<td>Human + ACD</td>
<td>FP M H R T B</td>
<td>Damage + Performance</td>
</tr>
</tbody>
</table>

E Series experiments

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Blood</th>
<th>Components in circuit</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Human $A^+$ + ACD</td>
<td>FP M H R T B</td>
<td>Damage + Performance</td>
</tr>
<tr>
<td>E2</td>
<td>&quot; $A^+$ &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E3</td>
<td>&quot; $A^+$ &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E4</td>
<td>&quot; $A^-$ &quot;</td>
<td>&quot;</td>
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<tr>
<td>E5</td>
<td>&quot; $A^+$ &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E6</td>
<td>&quot; $A^+$ &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E7</td>
<td>&quot; O$^+$ &quot;</td>
<td>&quot;</td>
<td>Effect of changing O$_2$ pressure</td>
</tr>
<tr>
<td>E8</td>
<td>&quot; AB$^+$ &quot;</td>
<td>&quot;</td>
<td>&quot; of changing blood flow</td>
</tr>
<tr>
<td>E9</td>
<td>&quot; B$^+$ &quot;</td>
<td>&quot;</td>
<td>&quot; of larger deoxygenator</td>
</tr>
<tr>
<td>E10</td>
<td>&quot; $A^+$ &quot;</td>
<td>&quot;</td>
<td>Damage + Performance</td>
</tr>
<tr>
<td>E11</td>
<td>Pig + EDTA</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E12</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E13</td>
<td>Bovine + EDTA</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E14</td>
<td>Human O$^+$ + ACD</td>
<td>&quot;</td>
<td>Vibration transients</td>
</tr>
</tbody>
</table>

Key:

- F - Film Oxygenator
- P - Pump
- M - Membrane Oxygenator
- H - Heat exchanger
- R - Reservoir
- T - Bubble trap
- V - Valves

From the above experiments the 18 graphs listed were drawn.
<table>
<thead>
<tr>
<th>Graph No.</th>
<th>Axes</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Plasma Hb. v time</td>
<td>Determine damage by pump</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot; circulation</td>
</tr>
<tr>
<td>3</td>
<td>Red cell count v Plasma Hb</td>
<td>Relate red cell count to Plasma Hb</td>
</tr>
<tr>
<td>4</td>
<td>Plasma Hb. v time</td>
<td>Determine damage by valves etc.</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>&quot; film ox.</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>&quot; vibration</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>&quot; film ox. cct.</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>&quot; membrane ox. cct</td>
</tr>
<tr>
<td>9</td>
<td>% Albumin v time</td>
<td>Determine protein alterations measurable</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>&quot; alterations for film ox</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>&quot; alterations for membrane ox</td>
</tr>
<tr>
<td>12</td>
<td>(A-V)SO₂ v blood flow</td>
<td>Determine effect of blood flow</td>
</tr>
<tr>
<td>13</td>
<td>Performance v &quot; &quot;</td>
<td>&quot; optimum blood flow</td>
</tr>
<tr>
<td>14</td>
<td>(A-V)SO₂ v time</td>
<td>&quot; pressure change transients</td>
</tr>
<tr>
<td>15</td>
<td>(A-V)SO₂ v pressure</td>
<td>&quot; effects of oxygenator pressure</td>
</tr>
<tr>
<td>16</td>
<td>(A-V)SO₂ v time</td>
<td>&quot; vibration change transients</td>
</tr>
<tr>
<td>17</td>
<td>(A-V)SO₂ v vibration f</td>
<td>&quot; effects of vibration</td>
</tr>
<tr>
<td>18</td>
<td>(A-V)SO₂ &quot;</td>
<td>&quot; &quot;</td>
</tr>
</tbody>
</table>
CHAPTER 4
EXPERIMENTAL WORK AND RESULTS

4. 1  Experiments to assess increases in plasma hemoglobin

4. 1. 1  Introduction

Four series of experiments were executed

a) P'1 - P12 - Pump tests
b) G1 - G6 - Component tests
c) F1 - F18 - Film oxygenator tests
d) M1 - M23 - Membrane oxygenator tests

The aims of these tests with reference to plasma hemoglobin were to:-

a) quantify the hemolysis rate for the pump and other circuit components alone in order to isolate the proportion of damage being done by the oxygenators
b) Ensure that damage was due to circulation of blood not merely its presence in the circuit.
c) quantify the increase in hemolysis rate attributable to active vibration of the oxygenator
d) compare the hemolysis rates of a film and a membrane oxygenator under identical tests
e) relate red cell count to hemolysis level.

4. 1. 2  Experimental Description

4. 1. 2. 1  Pump Tests

Two different techniques were used and these are illustrated below:

[Diagram illustration of a pump test setup]
The peristaltic pump speed and the pipe bore and length were identical in each experiment. For the first series P1 - P5 the pump direction was reversed each time a reservoir emptied. For the second series P7 - P9, P11, the rotation direction was maintained. In both, blood flow rate was checked by collection (95 ml/min). Samples were drawn at 30 minute intervals during tests lasting up to four hours and tested for plasma hemoglobin by the atomic adsorption method and plasma protein alteration by protein biuret and cellulose acetate electrophoresis methods. The blood was in all cases transfusion blood about three weeks old and in each case a microhematocrit was performed at stages during the experiment. At the end of each experiment the blood was allowed to stand for at least 30 minutes. The results are illustrated in graphs 1 and 2.

4.1.2.2. Component tests.

Experiments P6, P10, P12 and G1 - G2 were specifically designed to isolate the proportion of the hemolysis caused by individual components of the full test circuit.
The first three of these were designed to determine the hemolysis attributable to the film oxygenator.

**Expts. P 6, P 10, P 12.** (Room Temp.)

**Expts. G 1, G 2, M1 - M 23.**

**Expts. G 3 - G 5**

<table>
<thead>
<tr>
<th>RES</th>
<th>Reservoir</th>
<th>↑ Sampling point</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>Bubble trap</td>
<td>× Valve or clamp</td>
</tr>
<tr>
<td>HE</td>
<td>Heat exchanger</td>
<td>↑ Gas entry</td>
</tr>
<tr>
<td>MO</td>
<td>Membrane oxygenator</td>
<td>↑ Blood entry</td>
</tr>
<tr>
<td>FO</td>
<td>Film oxygenator</td>
<td></td>
</tr>
</tbody>
</table>

*Control*
Experiments G 1 and G 2 were carried out with bovine blood containing EDTA or ACD anticoagulant, as were all this series, at physiological temperatures with the full circuit. This included T pieces and clamps, had both oxygenators supplied with gas and, in the case of G 2, had the membrane oxygenator vibrating. Red cell and white cell counts were performed.

Experiments G 3 and G 4 were carried out without the membrane oxygenator. G 5 used valves instead of clamps. G 6 was performed with a nitrogen gas supply in place of air. In all six experiments, samples were drawn at 30 minute intervals and tested for plasma hemoglobin by Cripps' method. The results are illustrated in graphs 3 - 6.

4.1.2.3 Tests to compare Membrane to Film Oxygenators.

Experiments F 1 - F 18 and M 1 - M 23 were carried out with human transfusion blood, 3 - 4 weeks old, containing 120 ml ACD to 420 ml blood.

Expts. F 1 - F 18

Experiments M 1 - M 23 were performed using the circuit for experiments G 1 and G 2 with the oxygenator vibrating at differing rates.

In all experiments, temperature was maintained within 0.25 deg.C of physiological levels. The oxygenator gas supplies were adjusted to maintain PCO₂ between physiological limits. Blood pH in all experiments tended to fall and no attempt was made to rectify this chemically.
Blood samples were drawn at 30 minute intervals and tested for hemolysis by the cyanomethemoglobin method for total protein by the biuret method, for protein changes by electrophoresis, for $\text{PO}_2$, $\text{PCO}_2$ and pH levels using the BMS 3 instrument.

The hemolysis results are presented in Graphs 7 and 8.
4.1.4. Results of graphs

4.1.4.1 Graph 1

Graph of Plasma Hemoglobin level against circulation time
to quantify damage by pump.

The results gave a series of straight nearly parallel lines
suggesting that the damage caused to the red cells is a linear function
of circulation time and is independent of the blood type and initial
condition. The average damage caused was 6.8 mg.% per hour. Expt. P 2
gave a value three times this figure for no apparent reason although the
blood was found to be massively hemolysed on receipt (50.2 mg.%).

No significant increase was noticed on the control blood sample at
the end of any of the tests. No substantial differences were noticed
between tests carried out using continuous circulation into a single
reservoir and tests using alternate flow directions between two
reservoirs.

4.1.6.2 Graph 2

Graph of Plasma Hemoglobin level against Circulation time
to verify damage not due to mere presence of foreign surfaces.

The results gave three similar lines each with a straight, nearly
parallel section of slope about 7 mg.%/hr. becoming parallel when the
blood flow was discontinued. These show conclusively that the bulk
of hemolysis in the long term circulation is caused by the actual
circulation of the blood through the components of the circuit, not just
its contact with foreign surfaces. The nature of the surfaces though,
is of fundamental significance when an analysis of the shear forces on
the blood is made and the subsequent hemolysis studied.

4.1.4.3 Graph 3

In tests G 3 and G 6 the attempt to correlate the fall in
red cell count with the rise in hemolysis failed to produce any
significant relationship. The fall in hematocrit was also found to be
too small to be of any significance.

4.1.4.4 Graphs 4, 5

Graph of Plasma Hemoglobin level against Circulation time,
to quantify damage by other circuitry.

The results gave a series of straight lines emanating from the
origin, the slope of each depending on the components used in each circuit.
PLASMA
Hb
mg %
(atOMIC adsorption)

100
50

0

1
2
3
HOURS

GRAPH 1

TO QUANTIFY HEMOLYSIS DUE TO RESERVOIR, PUMP & TUBING
PLASMA Hb mg %
(atomic adsorption)

HOURS

0 1 2 3 4 5

TO PROVE DAMAGE IS DUE TO CIRCULATION

GRAPH 2

P9

P8

P5

TCS PROVE DAMAGE S T T
PLASMA
Hb
mg %
(Cripp's Method)

GRAPH 4

4.134 To show hemolysis due to components in circuitry
TO SHOW HEMOLYSIS DUE TO FILM OXYGENATOR
Tests G 3 and G 4 show a hemolysis rate of 15 mg.% per hour. Test G 6 which had a gas supply to the deoxygenator shows an increase to 17.4 mg.% per hour.

The inclusion of control valves in test G 5 shows a massive increase to 28 mg.% per hour.

The tests P 6, P 10 and P 12 show a hemolysis rate of 13.5 mg.% for the film oxygenator, pump and reservoirs.

4.1.4.5 Graph 6

Graph of Plasma hemoglobin level against Circulation time to determine damage by vibrator.

Blood was circulated through the stationary oxygenator for 90 minutes when a vibration of 400 Hz was applied. The results gave a straight line exhibiting no change of slope at the 90 minute point, implying that no marked increase in hemolysis occurs as a result of vibration.

4.1.4.6 Graphs 7 and 8

The full perfusion circuit was operated for between 3 and 5 hours using outdated transfusion blood. The hemolysis levels were calculated and plotted against the time the samples were drawn. Graph 7 illustrates the corresponding rise when the membrane oxygenator replaced the film oxygenator. Graph 8 shows a mean hemolysis rate of increase of 15 mg.% per hour for the membrane oxygenator circuit while Graph 7 shows a rate of 25 mg.% per hour.

Four tests from each of the F and M series are illustrated as being representative of the remainder.

4.2. Experiments to assess the alterations to plasma proteins and to relate these to hemolysis.

4.2.1. Introduction

Three series of experiments were performed to cover this aspect of the work.

a) P 1 - P 12
b) F 1 - F 18
c) M 1 - M 23

The aims of these tests with reference to plasma protein denaturation were to:-
To show vibration does not increase hemolysis
Graph 7 - To show increase in hemolysis with time - Film Oxygenator
To show increase in hemolysis with circulation time - membrane oxygenator.
a) quantify the protein denaturation, if possible for each of the circuit components.
b) to identify all changes in mobility and proportion of each discernable protein fraction.
c) to quantify the total protein loss from the circulating blood for each component of circuitry.
d) to correlate, if possible the rise in plasma hemoglobin with the loss of albumin

Tests P 1 - P 12 were designed to establish the protein alteration due to the circulation of blood through the pump alone. Tests F 1 - F 18 and M 1 - M23 allowed the film and membrane oxygenators to be compared for protein damage.

4.2.2. Experimental description - as in 4.1.2.

4. 2. 3. Graphs 9 - 11

4. 2. 4. Analysis of Graphs

4. 2. 4. 1. Graph 9. Graph of Albumin content against time.

The graph shows a fall in the percentage of albumin in the blood with time. This fall is much more marked when the film oxygenator is included in the circuit. The total protein content fell from 4.76 to 4.45 mg.% for the film oxygenator, a loss of 6.5%, whilst for the basic circuit containing only pump and reservoir, the drop was from 5.08 to 4.95 mg.% or 2.3% fall. In both cases there was an immediate fall in the percentage content of albumin attributed to the coating of the surfaces of the circuitry by the proteins. It is not uncommon for circuitry to be primed with albumin.

Only two of the twelve tests are represented in the graph. The protein alteration attributable to any individual component of circuitry was neither sufficiently large nor sufficiently consistent to be worth quoting. Aims 4. 2. 1. a, c, were not then achievable by the chosen measuring techniques.

4. 2. 4. 2. Graphs 10, 11.

The graphs are based on area measurement of the densitometer scans taken from paper electrophoretic examination of blood samples. These were drawn at 30 minute intervals. The 4 traces in fig. 11 represent four of the tests on the full perfusion circuit including the static membrane oxygenator. Those in figure 10 represent the same circuit with a film oxygenator replacing the membrane oxygenator. The film oxygenator
ALBUMIN %

To show reduction in proportion of albumin with circulation time

CONTROL

BASIC CIRCUIT

P10
To show reduction in proportion of albumin with time - Film Oxygenator
ALBUMIN %

4.2.3.3  Graph 11

To show reduction in proportion of albumin with time – membrane oxygenator
gives an average fall of 1.3% per hour while the membrane oxygenator gives 0.7% per hour.

The effect of changing oxygenators is to decrease the proportion of albumin by 0.6% per hour. Measurements were also taken to observe any alterations in mobility of the protein fractions. Only the $\alpha_2$ fraction exhibited any definite trend, its mobility increasing in the case of the film oxygenator.

There is a link between the increase in plasma-hemoglobin level and the corresponding decrease in albumin level. Comparing graphs 7 and 10 Tests 10 F and 17 F for example exhibit this pattern.

4.3. Experiments to assess methods of improving oxygenator performance.

4.3.1 Introduction.

Two of the series of experiments performed contained at least an element of performance measurement relevant to the membrane oxygenator.

a) M 1 - M 23
b) E 1 - E 14

The improvement of oxygenation performance by the following methods was examined.

a) determination of optimum flow rate
b) pressurization of oxygen phase
d) vibration of the oxygenator

Finally the time taken for the system to settle, following sudden changes in operating conditions, was studied.

4.3.2. Experiment Description

Experiments M 1 - M 23 were as described in section 4.1.2.3. All these were executed with the membrane oxygenator vibrating at frequencies ranging from 0 - 400 Hz.

Experiments E 1 - E 6, E 10, and E 14 were used identical apparatus to the 'M' series. Experiments E 11 - E 13 used animal blood with EDTA (Pig or Bovine) but the same circuit.

Experiment E 7 explored the effect of changing oxygenator gas pressure, experiment E 8 of changing pump setting (blood flow rate) and E 9 of inserting a larger film deoxygenator.

4.3.3. Graphs 12 - 18
A-V
SOC \% 12

4.3.3.1  GRAPH 12

TO SHOW RELATION BETWEEN MEMBRANE OXYGENATOR PERFORMANCE AND BLOOD FLOW
MEMBRANE OXYGENATOR PERFORMANCE vs BLOOD FLOW
Graph 14
To show response time following change of oxygen pressure

- 39 mm Hg
- 50 mm Hg

SO₂ %
To show effect on gas transfer of pressurising oxygen supply.
To show response time following commencement of vibration.
Graph 17

To show enhancement of membrane oxygenator performance by vibration

(for single experiment)
Graph 18

Arterial - Venous Oxygen Saturation v Vibration Frequency

(12 experiments, 27 data points)
4.3.4 Analysis of Graphs

4.3.4.1 Graph 12

Graph of A - V oxygen saturation against blood flow rate

The graph based on data from experiment E 8 shows an approximately linear decrease in A - V oxygen saturation (SO₂) difference.

4.3.4.2 Graph 13

Oxygenator performance against blood flow rate

The graph exhibits an optimum performance at a flow rate of 50/ml/min.

4.3.4.3 Graph 14

A - V saturation difference (SO₂) against time. Change in oxygen pressure.

The experiment was based on an idea explored by Dagher that not only can advantage be gained over the natural lung by breathing pure oxygen but also by pressurizing the oxygen to yield an even greater difference in partial pressures between the gas and blood phases. The pressures chosen lay on either side of the pressure of the blood in the oxygenator. The greater pressure required a glass fibre support in the blood phase.

The graph shows a fall in A-V saturation from 8% down to 3%. This represents a 62% drop for a pressure change of only 1.7%.

4.3.4.4 Graph 15

Graph of A - V saturation difference (ΔSO₂) against oxygen pressure.

The graph shows a similar trend to Graph 8 A. For pressures below the blood pressure in the oxygenator, the A - V saturation difference is markedly reduced.

4.3.4.5 Graph 16

Graph of A - V oxygen saturation against time (to exhibit the effect of commencing vibration).

The graph was produced from data from experiment E 14 and is typical of all similarly conducted tests. The restoration of steady conditions following the commencement of vibration required nearly 60 minutes. The transient characteristics were approximately exponential with a time constant of approximately 20 minutes.

4.3.4.6 Graph 17

Graph of A - V oxygen saturation difference against vibration speed - single experiment.

The graph was produced from results taken from a single experiment in which the oxygenator was vibrated at successively higher speeds.
The arterial and venous saturations were recorded following steady conditions. The time taken for such conditions to be reached made it impossible to take more than four or five readings to be obtained.

The graph is approximately linear showing marked improvement of performance by the use of vibration. A fourfold increase can be observed for a vibration speed of 400 Hz. A very similar increase for the same vibration speed was discovered by Illickal on a very different experiment.

4. 3. 4. 7 Graph 18

Graph of A - V oxygen saturation difference against vibration speed - 27 data points.

The graph was produced from results taken from 12 experiments. In each experiment blood was oxygenated at a fixed rate for up to two hours to ensure steady conditions.

The graph is approximately linear with a scatter of up to 30%.
5.1 Theoretical Analysis of Gas Transfer.

The process of gas exchange through a polymer membrane was shown by Bell and Grosberg (1961) to be mainly a process of diffusion which under steady conditions obeys Fick's first law:

$$ Q = \frac{D' P}{t} $$

where $Q$ is the gas flow rate per unit area in ml./min.m$^2$, $D'$ is the membrane diffusion coefficient in ml.mm$^2$/min.mm.Hg, $t$ is the film thickness in mm, and $P$ is the pressure gradient in mm.Hg.

The diffusion coefficients for silicone rubber as determined by several authors is tabulated below. Since there is no agreement on the units, these have been compared for a partial pressure gradient of 650 mm.Hg. and a membrane thickness of 0.0015 in. (0.0381 mm.).

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Material/Thickness</th>
<th>$D'_O_2$</th>
<th>$\frac{D'_CO_2}{D'_O_2}$ (40mm)</th>
<th>Conversion Factor</th>
<th>Oxygen Transfer ( \text{mL/m}^2\text{min.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silastic® 50</td>
<td>2600x10$^{-11}$</td>
<td>0.25-0.31 (4.5)</td>
<td></td>
<td>266</td>
</tr>
<tr>
<td>2</td>
<td>Silastic S-2000</td>
<td>5890x10$^{-11}$</td>
<td>650x10$^{-11}$</td>
<td>1.023x10$^{10}$</td>
<td>603</td>
</tr>
<tr>
<td>3</td>
<td>Dimethyl silicone</td>
<td>60x10$^{-9}$</td>
<td>0.35(5.4)</td>
<td></td>
<td>614</td>
</tr>
<tr>
<td>4</td>
<td>Rubber 6.5mil.</td>
<td>10,005</td>
<td></td>
<td>0.0405</td>
<td>405</td>
</tr>
<tr>
<td>5</td>
<td>Silastic 3 mil.</td>
<td>300</td>
<td>0.27(4.4)</td>
<td>20</td>
<td>600</td>
</tr>
<tr>
<td>6</td>
<td>Silicone 1 mil.</td>
<td>1200</td>
<td>0.27(4.4)</td>
<td>0.667</td>
<td>800</td>
</tr>
<tr>
<td>7</td>
<td>Silastic 3 mil.</td>
<td>350</td>
<td>0.27(4.3)</td>
<td>1.711</td>
<td>600</td>
</tr>
<tr>
<td>8</td>
<td>Methyl Silicone 1 mil.</td>
<td>1092</td>
<td>0.33(5.3)</td>
<td>0.570</td>
<td>622</td>
</tr>
<tr>
<td>9</td>
<td>Silicone Rubber 1/2 mil.</td>
<td>520</td>
<td>0.34(5.3)</td>
<td>0.855</td>
<td>608</td>
</tr>
</tbody>
</table>

1. Kammermeyer (1957)  
2. Dow-Corning data sheet (1960)  
3. McCaughan (1960)  
4. Melrose (1972)  
5. Benvenuto (1959)  
6,7,Galletti,Snider & Silbert-Aidant (1966) ml/m$^2$ min. 650 mm.Hg.  
8,9,Peirce & Dibelius (1968)  
While these values vary from the lowest to the highest by a factor of 3, most give a maximum oxygen transfer rate through 1.5 thou (0.0381 mm.) of silicone rubber of about 600 ml./m²/min for an effective partial pressure gradient of 650 mm.Hg. The equivalent figure for carbon dioxide transport assuming a partial pressure gradient of 40 mm. Hg is 180 ml./m²/min.

5. 1. 2. Gas Transport by Blood.

5. 1. 2. 1. Oxygen

5. 1. 2. 1. 1. Dissolved in plasma

Plasma contains 0.023 cc. of oxygen per millilitre when the partial pressure of the oxygen is 760 mm. Hg. At different pressures it contains a proportionate amount:

\[
\text{Dissolved oxygen} = 0.023 \times \frac{P \text{O}_2}{760} \text{ cc/ml.} \quad \text{(Davenport)}
\]

The maximum physiological \( P \text{O}_2 \) is about 100 mm. Hg, given a corresponding dissolved oxygen level of 0.3 ml.%. This falls to 0.12 ml.% in the veins (Passmore).

In an artificial lung however pure oxygen (assumed wet) may be breathed giving for a venous \( P \text{O}_2 \) of 40 mm. Hg, an effective partial pressure gradient of:

\[
760 - 47 - 40 = 673 \text{ mm. Hg.}
\]

Since the partial pressure of water vapour, 100% saturated, is 47 mm. Hg, this is equivalent to 2 ml.% of oxygen in the plasma. A pressurised oxygen supply could increase this figure.

5. 1. 2. 1. 2. Combined with hemoglobin.

The quantity of oxygen carried in chemical combination with hemoglobin also depends on \( P \text{O}_2 \).

1 mole \( \text{O}_2 \) (32 grams) combines with 16,700 g. of Hb. (\( M = 67,000 \)) and occupies 22,400 ml.

1 gram of Hb. therefore combines with 1.34 ml. \( \text{O}_2 \) (Passmore quotes 1.38 ml \( \text{O}_2 \) per gram of Hb).

The percentage oxygen saturation, \( S \text{O}_2 \), is related to the partial pressure of oxygen \( P \text{O}_2 \) by the following equation

\[
S \text{O}_2 = \frac{100 k P \text{O}_2}{1 - k P \text{O}_2}
\]

where \( k \) is a constant.
It suggests a hyperbolic curve but in fact, because of the oxygen dissolved in plasma it is a sigmoid.

\[
S_{O_2} \quad P_{O_2}
\]

(Davenport)

Aberman quotes an equation for this curve.

At \(P_{O_2} = 100 \text{ mm Hg}\), \(S_{O_2}\) is nearly 100%. If the hemoglobin content of the blood is 14.5 gm% (Sandoz), then the maximum oxygen content \(C_{O_2}\) of blood is:

\[
C_{O_2} = (14.5 \times 1.34) \text{ ml}% + 0.3 \text{ ml/} = 20 \text{ ml %}
\]

hemoglobin plasma total

\[O_2\] tension - 35 mm

\[\text{arteriole}\]
- \(O_2\) tension - 100 mm
- \(O_2\) in cells - 19 cc
- \(O_2\) in solution - 0.8 cc
- \(SO_2\) - 95 cc
- \(CO_2\) tension - 40 mm

\[\text{venule}\]
- \(O_2\) tension - 40 mm
- \(O_2\) in cells - 15 cc
- \(O_2\) in solution - 0.15 cc
- \(SO_2\) - 75 cc
- \(CO_2\) tension - 46 mm

after Samson Wright
In the veins where the $P_{O_2} = 40 \text{ mm.Hg}$ (say), $C_{O_2}$ could be as low as 8 ml.% hence the oxygenator would have to supply the balance of 12 ml%. For a body content of 5 litres pumped in one minute at rest, 600 ml/min. must be transferred by the oxygenator. In practice, however, the saturation may only vary between 70% and 95%, reducing this demand to 250 ml/min.

The sigmoid curve of $S_{O_2} v P_{O_2}$ is pushed to the right when the carbon dioxide content of the blood is increased, when the temperature rises, when the pH falls and when the HbCO level falls. Active tissue has a high $P_{CO_2}$, low pH and raised temperature, all aiding the release of oxygen for its respiration.

Corrections to the oxyhemoglobin dissociation curve for temperature and pH deviations can be made using the nomogram below:

<table>
<thead>
<tr>
<th>Temp. Factor</th>
<th>pH Factor</th>
<th>$SO_2% P_{O_2}$</th>
<th>$SO_2% P_{O_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^\circ C$</td>
<td>pH</td>
<td>$P_{O_2}$ multiplier</td>
<td>$P_{O_2}$ multiplier</td>
</tr>
<tr>
<td>40</td>
<td>7.0</td>
<td>0.5</td>
<td>40</td>
</tr>
<tr>
<td>35</td>
<td>6.9</td>
<td>0.6</td>
<td>55</td>
</tr>
<tr>
<td>30</td>
<td>6.8</td>
<td>0.7</td>
<td>70</td>
</tr>
<tr>
<td>25</td>
<td>6.7</td>
<td>0.8</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>6.6</td>
<td>0.9</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>6.5</td>
<td>1.0</td>
<td>120</td>
</tr>
<tr>
<td>10</td>
<td>6.4</td>
<td>1.1</td>
<td>140</td>
</tr>
<tr>
<td>5</td>
<td>6.3</td>
<td>1.2</td>
<td>160</td>
</tr>
<tr>
<td>0</td>
<td>6.2</td>
<td>1.3</td>
<td>180</td>
</tr>
</tbody>
</table>

Dissociation Curve pH 7.4, 37°C
5.1.2.2 Carbon Dioxide

5.1.2.2.1 Dissolved in Plasma and Red cell

Dissolved carbon dioxide amounts to 1.6 - 1.8 ml% in plasma for a \( P_{CO_2} \) of 40 mm Hg, and 0.8 - 0.9 ml% in the red cell. Carbon dioxide is much more soluble than oxygen.

5.1.2.2.2 As bicarbonate

90% of carbon dioxide is carried as sodium bicarbonate (34-36ml%) in plasma and as potassium bicarbonate (9.1 - 9.9 ml%) in the red cell.

5.1.2.2.3 Combined with Proteins

Carbon dioxide forms a neutral carbamino compound with hemoglobin and to a much lesser extent with the plasma proteins. Unlike oxygen which attaches to the haem radicals, carbon dioxide combines with the amino groups. The physiological levels vary from 2.2 ml% in the arteries to 3.2 ml% in the veins.

The table below summarises the distribution of carbon dioxide (ml) in 100 ml of blood in a subject at rest for a hematocrit of 40% and a pH = 7.4 (adapted from Henderson B.D.S.)

<table>
<thead>
<tr>
<th></th>
<th>ARTERY</th>
<th>VEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>R.B.C.</td>
</tr>
<tr>
<td>Dissolved ( CO_2 )</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>( CO_2 ) as bicarbonate</td>
<td>34.</td>
<td>9.1</td>
</tr>
<tr>
<td>Carbamino compounds</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>36.7</strong></td>
<td><strong>12.1</strong></td>
</tr>
</tbody>
</table>

Reduced blood takes up more carbon dioxide at the same \( P_{CO_2} \) than oxygenated blood because reduced hemoglobin has a greater capacity for buffering and carbamino - carbon dioxide formation.

For a \( P_{CO_2} = 0 \) all the carbon dioxide is released, unlike a simple bicarbonate solution which would leave half as bicarbonate.

Summarising, the carbon dioxide level in veins for a \( P_{CO_2} = 40 \text{ mm.Hg} \) is 53 ml%, 75% of which is carried in the plasma. This is reduced to 48% in the arteries where the \( P_{CO_2} = 46 \text{ mm.Hg} \), hence the lung must remove 205 ml\( \text{CO}_2/\text{min.} \) for a blood volume of 5 litres pumped each minute. The major reactions which take place when gas exchange occurs between blood and alveolar gas (after Bell, Davidson & Scarborough) are shown overleaf:
5.1.3 Gas Transport Through Plasma

The passage of oxygen through plasma obeys Fick's law

\[ Q = \frac{D'}{t} \text{ as before} \quad \text{-- (equation 1)} \]

The permeation coefficient, \( D \), for plasma is generally agreed to be of the order of \( 6.5 \times 10^{-10} \text{ ml. O}_2 \text{ cm/cm}^2 \text{s mmHg} \), 10 times bigger at \( 60 \times 10^{-10} \text{ ml. O}_2 \text{ cm/cm}^2 \text{s mmHg} \).

It is vital then in a membrane oxygenator either that the blood film thickness (t) is made very small or that intimate mixing of erythrocytes and plasma is achieved.

Equation 1 can be rearranged

\[ P = \frac{Q (t)}{D'} \]

Cf. \[ V = I \times R \text{ electrical} \]

(Potential Drop) \[ = \text{(Current Flow) x (Resistance)} \]

These two equations are analogous, \( P \) and \( V \) representing pressure drop and electrical pressure drop respectively, \( Q \) and \( I \) being the flow rates of gas and electrical current respectively and \( \frac{t}{D'} \) and \( R \) both representing resistance to flow.

In the lung, diffusion in the plasma accounts for 15% of the total resistance in the process of oxygenation and about 30% of the blood's proportion of this (the alveolar capillary wall represents the other 45% of the total - Roughton and Rupp 1958). It is reckoned that in the artificial lung, plasma could represent over 70% of the blood's proportion of resistance.
Carbon dioxide also obeys Fick's law but $D$ for carbon dioxide is probably 85% of $D$ for oxygen since the rate of diffusion of dissolved gases is proportional to the square root of their molecular weight ($\sqrt{32/44} \approx 0.85$). The solubility coefficient ($a$) of carbon dioxide in plasma though is 25 times that of oxygen so that $D' = axD = 139 \times 10^{-10}$ ml/cm/cm$^2$/s mm Hg.

The $P_{CO_2}$ of venous blood, 46 mm Hg, is approximately the same as the $P_{O_2}$, so being 25 times as soluble in plasma, carbon dioxide should transfer at up to 25 times that for oxygen. In an artificial lung, however, where the $P_{O_2}$ gradient may be 650 mm Hg, about 14 times that for $C_{O_2}$, carbon dioxide will diffuse only twice as fast as oxygen.

5.1.4. Gas Transfer in the Red Cell

The gas transfer into the cell consists of diffusion through the cell membrane, diffusion through the cell interior and finally chemical combination with hemoglobin. The relative resistances of these processes to oxygen and carbon dioxide are shown below:

<table>
<thead>
<tr>
<th></th>
<th>$O_2$ 40 mm.Hg</th>
<th>$CO_2$ 40 mm.Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem. Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffusion in R.B.C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membrane</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

100 mm.Hg

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$CO_2$ 46 mm.Hg</td>
</tr>
<tr>
<td>Chem. Reaction</td>
</tr>
<tr>
<td>Diff. in R.B.C.</td>
</tr>
<tr>
<td>Membrane</td>
</tr>
</tbody>
</table>

(Adapted from Roughton & Rupp 1958)

The diagrams are not intended to imply that there is equal total resistance to the transfer of each gas.

If the gas pressure gradient is increased the diffusion processes are accelerated and the proportions affectively change since the speed of chemical reaction does not. (Mochizuki 1,2) In the lung, the resistance
of the red blood cell to the process of oxygenation contributes 37% of the total while to the process of carbon dioxide elimination, it represents 87%.

To summarise, in the artificial lung, the chief barriers to oxygen transport over which we may have some measure of control are the red blood cell and more importantly, the plasma. For carbon dioxide, however, the lung membrane forms the greatest barrier—we have little control over the speed of chemical reaction in the red cell. All that can be done then as far as carbon dioxide is concerned is to use the smallest safe thickness of membrane of as high a permeability as possible. For oxygen transport either the blood film should be as thin as possible or a way be found of presenting each red cell in intimate contact with the membrane surface.

In a sandwich type membrane oxygenator it is theoretically possible to present 32,000 red cells per square millimetre at any one time. If only one millisecond is necessary to equilibrate this layer with oxygen and it were possible to instantly replace this with further layers requiring oxygenation, then only one sixth of a second would be required to completely oxygenate a 1 mm thickness of blood film. Theoretically then, the plasma would pose no barrier at all.

For a finite blood thickness, the flow rate of oxygen under steady conditions is given by

\[ Q = \frac{P}{R} \]

\[ R = \frac{t_m}{D_m} + \frac{t_v}{D_v} = \text{total resistance of blood and membrane combined to gas transfer.} \]

The proportion of these two resistances to the transfer of oxygen and carbon dioxide is illustrated in graphs 19 and 20.

5.5. Comparison of Analysis and Practical Work

Graph 20 illustrates clearly the penalty of loss of efficiency incurred by using a static system with a definite blood film thickness.

The theoretical maximum gas transfer for the model oxygenator could be calculated as follows:-

- Membrane area \( = 2 \times 63 \times 140 \text{ mm}^2 = 17,640 \text{ mm}^2 \)
- Blood film thickness \( = 0.25 \times 25.4 \times 1000\mu = 6,300\mu \)
- Membrane thickness \( = 1.5 \text{ thou} = 0.038 \text{ mm} \).
Specific Flow Rate
ml/m² min

Resistance

Blood Film Thickness μm

Resistance of Blood Film

Resistance of Membrane

GRAPH 19

Carbon Dioxide Transfer through 100 μm Membrane

(under 46 mm Hg)
Graph 20

Oxygen Transfer Through 117thou Membrane (under 650 mm Hg)
This data would yield a theoretical oxygen specific flow rate of less than 1 ml/m²-min. However, the natural mixing caused by the turbulence at entry to the blood chamber by the roughness of the membrane and in some cases by the interposition of a blood screen raised this to between 20 and 30 ml/m²-min.

The introduction of secondary flows by the introduction of external vibration of the oxygenator increased the performance beyond 100 ml/m²-min. Graph 20 suggests that this level of performance is consistent with elimination of plasma as an effective barrier - probably by the hoped-for recirculation of red cells across the boundary layer.
CHAPTER 6

AN APPRAISAL AND SUGGESTIONS FOR FURTHER WORK.

6.1 Appraisal of the work

6.1.1 The blood.

The majority of experiments were conducted with human transfusion blood between three and four weeks old containing 22% ACD. The blood was generally in good condition, only two bottles being found well hemolysed on receipt. It is appreciated that erythrocyte life span is around 120 days but the cold storage of blood for about 25 days did not appear to give a pro-rata increase in dead cells. 'Analogous' fluids, even animal blood, were avoided as being clinically of doubtful relevance. Animal blood was found to be of unreliable quality. It was thought essential in studying the effect of vibration and other parameters on oxygenation rate and of circuitry on blood damage to use whole blood. The erythrocytes as discussed in Chapter 5 are the major oxygen carrying constituent and in view of their strange flow characteristics in plasma (sigma effect) their presence is vital.

It was also considered essential to simulate physiological conditions as nearly as possible - Physiological temperature and gas partial pressures were maintained although pH was found difficult to control and tended to fall. It is appreciated that this in itself could effect results especially those concerning hemolysis. An adjustment was made for pH alteration in the calculation of oxygen transfer.

The presence of ACD in the blood in much higher proportions than would be found during bypass operations has the effect of reducing damage by reducing the concentration of erythrocytes. As far as oxygenation is concerned, though, the effect of ACD is to increase the plasma barrier and reduce efficiency.

The reasoning behind in vitro testing is discussed in 2.3

6.1.2 Haemolysis

The importance of hemolysis control lies in the appreciation of its role in increasing sludging and the likelihood of renal or cerebral failure due to embolism. The massive rates of hemolysis which a healthy body can tolerate cannot be swept up by the reticulo-endothelial system of a patient under bypass conditions.

Hemolysis has been shown to be due predominantly to the circulation of the blood through the components of the circuit not merely its contact
with foreign surfaces. Components which cause a sudden change of flow rate aggravate red cell damage and there is some evidence that gas contacting devices also increase this form of damage. Numerical results for the hemolysis attributable to each component of circuitry used in this series of experiments appear in Section 4.14.

The hemolysis caused by the membrane and film oxygenator circuits were respectively 15 mg.% and 25 mg.% The former figure, while the lower is too high for a practical perfusion circuit and although the circuit contained a film deoxygenator and other non-ideal components, the membrane oxygenator itself was partially responsible. Although some care was taken in the design of the oxygenator, this was chiefly for the convenience of easy construction and of change in parameters like blood chamber thickness. It is thought possible to design a membrane oxygenator whose hemodynamics are sufficiently simple to minimise hemolytic damage. Vervloet (1970) claims this for the Landé-Edwards membrane oxygenator.

Screens in the blood phase, as suggested by Bramson (1965,1972) were used in an early attempt to create secondary flows and improve efficiency. There was evidence of improved gas transfer using an annealed glass fibre screen but massive hemolysis resulted. There was no evidence of increased blood damage by external vibration. Hickel (1967) whose spinning technique might have been expected to increase hemolysis did not observe any marked rise. In fact, no worker has, in the field of secondary flows (for the improvement of oxygenation) observed any significant detrimental effect (Alton Murphy 1971).

6. 1. 3 Protein Denaturation

Lee (1971) has discussed in some detail the effect of denaturation on the primary secondary and tertiary structure of proteins. He has claimed (Lee 1) that membrane oxygenators have a lower tendency to promote denaturation than their gas-contacting counterparts and that denaturation can cause complications or death following bypass (Lee 2).

Kayser (1974) claims that the evidence for significant denaturation in any modern blood-gas interface oxygenator at physiological gas tensions and temperatures is thin. Wright (1962) failed to demonstrate any significant protein denaturation in screen or membrane oxygenators.
This thesis attempted in part to re-examine the effect of extra-corporeal circulation on plasma proteins. Using available apparatus, the convenience of the protein biuret procedure and cellulose acetate electrophoresis to determine changes in the relative protein fractions was attractive. Starch or other gel techniques would have given better definition but was more expensive, time consuming and difficult to analyse quantitatively.

There did appear to be a greater decline in the relative albumin content of the serum for the film oxygenator circuits (1% per hour) than for the membrane oxygenator circuit (0.6% per hour). The changes were small and the significance of the reduction is not fully appreciated. There also appeared to be an increase in the mobility of the $\alpha_2$ fraction with little measurable change in the remainder. All these finding were observed by Wright (1962). Lee (2) also noted the albumin loss caused by an artificial circulation.

There was an initial loss of protein on priming the circuit mainly of albumin. Thereafter the total protein level fell only slightly.

6. 1. 4. Vibration

The control of the hemodynamics of the erythrocytes by vibration and by the design of circuitry can greatly enhance oxygen transfer. The attempt is to reduce the resistance to gas flow by eliminating the effective resistance of the plasma. This ability has been demonstrated by Illickal (1967), Melrose (1) and others. Many techniques have been employed but there is no precedent for vibrating a conventional static bed oxygenator to improve gas transfer. Vibration in a plane, perpendicular to the membrane, proved to give similar improvement to that shown by other workers on widely differing systems. If, as suggested by this series of experiments, vibration causes improved oxygenation with no apparent adverse effects, current, clinically-used, static membrane oxygenators like the Travenol, Landé-Edwards and G.E.C. Peirce could have their performance increased and their size reduced. The benefits would be a more compact machine, possibly portable, producing less damage and costing less to operate.

The mechanism which caused this improved performance is not known but it appears from the quoted hematocrit figures (on graph) that this may not be explained away by changes in the affinity of the blood for oxygen. There are a number of possible mechanisms, though, which might be relevant.

While it has often been thought desirable to maintain laminar flow conditions, many workers have found little damaging effects by imposing a relatively high flow rate on blood. Through the blood screen where the membrane presents a rough tacky surface, it is most unlikely that truly laminar flow could be established (Nikuradse's work on rough pipes). Certainly
where lateral vibration is brought into play, the random and erratic motion which is superimposed on the mean velocity of a point in turbulent flow is likely to be more pronounced. Small quantities of fast moving liquid will move sideways into a slow layer increasing the momentum of the latter. A corresponding motion of the slower fluid into the fast layer must take place to avoid accumulation. This lateral exchange of fluid would result in a similar eddying of cells whose intimate contact, with the membrane wall, however short, is so essential to efficient gas transfer. Certainly such momentum exchanges must lead to the breakdown of any cell depletion layer which establishes itself and whose existence presents high resistance to oxygen transfer.

The explanation may be simpler. In view of the vastly differing densities of the cells from their environment, the momentum given to a cell by lateral vibration may enable it to traverse layers of fluid and ultimately present itself to the membrane boundary.

The study of the effect of forced vibrations on the moving blood stream is a complex one. The membrane itself is elastic though not perfectly so. It was supported by a soft sponge which allowed a distortion of membrane shape and of the blood flow pattern. The motion of the membrane is forced by the movement of its edge supports. The resulting deflection might be difficult to analyse but the analysis used for the deflection of thin shells may closely approximate. The rheological analogue which one could contruct to simulate the mechanism of vibration might consist of a spring, mass, dam system for the membrane giving a motion of the centre of the membrane of the same frequency as the membrane supports but of differing phase. This phase shift would vary from zero at the support to a maximum at the membrane centre, each point on the membrane trying to impose its own motion on the adjacent fluid. The fluid, also essentially a spring, mass, damper system will in turn respond but with further phase shifts. The net effect will be to produce a layer of fluid with cells vibrating across it with differing phases and therefore differing velocities. At any given cross section, the phase lag between the membrane wall and the adjacent fluid will tend to cause the relative motion of blood cells to be directed towards the membrane wall whilst the membrane is accelerating and away whilst the membrane is decelerating. This action may well enhance gas transfer by eliminating an accumulation of saturated cells at the fluid boundary. There may also be an effect on the tethering of cells observed by Blackshear where vibration might prevent the establishment of this phenomenon.

Alternatively the vibration of the fluid boundary may set up lateral pressure waves across the medium causing regions of relatively high and of
relatively low pressure with a resulting change in the relative positions of
the fluid molecules. Again the effect would be to eliminate an accumulation
of saturated cells at the boundary and to enhance mixing. A complication
to the flow pattern is the relatively massive weight of red cells. Left to their
own devices, even in a moving stream, there would be a tendency for these to
gravitate to the lower membrane wall. The effect of vibration may be to
constantly repel cells from the lower surface like peas on a drum and hence
cause an interchange.

The mechanism may alternatively be due to the entry conditions to the
distorted blood layer where blood flow is forced to negotiate a bend on entry
producing lateral cellular motion under centrifugal action (Taylor vortices).

Whether any or a combination of the above mechanisms is operative in
enhancing oxygenation performance requires further study - possibly by flow
visualisation of heavy particles in an analogous medium. It is thought not to
be due to any alteration in the blood's affinity for oxygen nor can it be
attributed to suggested variations in initial blood quality. Certainly the
optimization of vibration technique is important and the possibility of ultimate
elimination of blood screens in flat bed oxygenations could have an important
beneficial effect.

The increase in oxygenation was a linear function of vibration frequency
and was approximately fourfold at 400 Hz. The implication is
that the performance could be improved further at yet higher frequencies. Unfortunately, although provision was made to use a signal generator to explore the higher range of frequencies - amplitude control was lost.

6. I. 5. Other Considerations.

It was noted during the course of the experiment that the 'time constant' of the transient response of the oxygenator to any change of parameter, vibration speed, oxygen pressure on flow rate, was of the order of twenty minutes. This would make management of perfusion difficult and push Longmore's dream of the 'two-control portable box' further into the future.

Experiments on the pressurization of the gas phase in an attempt to improve oxygenation showed a twofold increase in gas transfer for pressures exceeding the blood pressure. The effect is not proportional to the blood pressures involved but much greater. The reason for this is not fully understood although it is in part due to the reduction of the blood film thickness by the external pressure on the membrane. Work by Dagher (1959) showed pressurization caused oxygenation enhancement but the technique is frequently criticized on the grounds that it increases the dangers of air embolism. It was thought that pressurization might minimise the known adhesion of erythrocytes to the membrane surface. It was hoped that electron micrographs might be used to show this effect. The prints, however, proved inconclusive.

There appeared to be a linear decrease in oxygenation with increased blood flow rate. When replotted at oxygenation performance against blood flow a curve was produced which suggested an optimum flow rate giving maximum performance. Oxygen flow rate could not be shown to affect the oxygenators performance but the smallness of the membrane area made small changes difficult to detect. There was no detectable deterioration in oxygenator performance although small thrombi were occasionally seen to develop near the entry of the blood chamber. Vibration had the effect of minimising these and no thrombi were usually visible.

Various forms of membrane support were tried. The metal screens, although giving good support, severely decreased the effective membrane area, in one case by over 50%. Sponge supports proved most satisfactory although they prevented the viewing of the blood flow pattern.
Blood screens of various kinds were tried, these are highly necessary in the control of blood film thickness, a vital parameter if no secondary flows are imposed. Most increased hemolysis but by marginal amounts.

Other blood damage measurements were attempted. Hematocrit and erythrocyte counts fell during all experiments but too slightly to be significant. White cells were cleared from the blood, probably by adhesion to the circuit walls, within two minutes of induction into the circuit.

6.2. Suggestions for further work.

The greatest need is for the selection of instrumentation and tests which are consistent, reliable and minimise time. The acceptability of the atomic adsorption method for plasma iron determination has not been shown satisfactorily and it is suggested that several methods of hemolysis assay be attempted simultaneously for detailed comparison.

There are also many feasible methods for examination of protein denaturation (Kauzman 1959) and these require full exploration. The effect of denaturation of proteins on the body is not well understood nor is the control of denaturation.

Continuous oxygen saturation monitoring should be employed for future tests. The use of the Radiometer BMS 3 is time consuming and allows readings at best every five minutes. It also suffers from human errors introduced by the drawing of the sample. Oximetry has long been employed to monitor oxygen saturation. It was once common practice to determine the arterial $SO_2$ of a patient before a major operation using an ear oximeter. The principle of the oximeter (Reichert 1966) is colorimetric using either reflected or transmitted light. Systems for continuous monitoring are described by Blumenfeld (1973) and Clerbaux (1973).

Better knowledge of the hemodynamics of the red cell in secondary flows is required in order to enable design criteria to be formalised. Current research is by serendipity. A design is produced, parameters are changed and the effect noted - there is no unifying line to the research. Possibly the simulation of the red cell movement by particles in an analogous fluid whose motion could be better observed through the vibrating oxygenator or a simulation of it would produce firmer ideas.
The effect of changing the amplitude and frequency of vibration of currently used static-bed oxygenators to enhance their performance requires fuller investigation. The higher frequencies could be explored to determine the point at which the oxygenation transfer rate saturates or at which blood trauma rapidly increases.

The promise for the future makes the pursuit of the ideal oxygenator worthwhile. Operations which are not now clinically viable may become routine. Where time is at a premium, the membrane oxygenator may be able to buy that time. Economically, it will never be able to compete with its rivals and will only succeed if its superiority and reliability are proved beyond doubt.
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Blood Gas Analysis  (see also oximetry)

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Bramson Lung

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- Extracorporeal Circulation

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- A model of mass transfer in respiratory systems: Warner (1) 1969
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- Low order approximation for membrane oxygenators: Lightfoot (1) 1968
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Test and development of __ for cardiopulmonary assist.

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Development of __.

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Centrifugal __.

____ A new approach.

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x Long term __.

x Function of the perfused liver.

x Perfusion of the liver in vivo and in vitro.

x Perfusion of the pregnant sheep uterus.

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x Function and hemodynamics of __.

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Morphology following vv perfusion of __.

Review of 23 __ transplants.

x Perfusion apparatus for __ fix.

Membrane oxygenator for support of transplant __.
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x Clinical experience with hypothermia
x Theory and function of the membrane lung
___ its excuse, status and promise
Clinical use of ___
Moving rod ___
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Extracorporeal ___ 80 cardiac operations
Progress in design of ___
Engineering view and progress report
Current status in ___
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Gott (3) 1969
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Peirce (15) 1971
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Hydrogen peroxide as an oxygen source in __

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  - Theory of ionic diffusion through ___
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  - Ways to render ___ antithrombogenic
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- Optimization of collagen dialyses

- Ultrathin silicone polymer ___
  - Polyalkylsulfone - a new polymer for MO
  - Improved silicone ___
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- Study of ___ permeability in hemodialysis
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  - Gas permeability of plastics ___
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- Model of otolith
- Comparison of gas transfer capabilities
- Lysobarism-osmosis caused by dissolved gas
- Development of ultra-thin teflon
- Testing device for gas transfer evaluation
- Comparison of gas transfer
- Evaluation of dialysis
- Evaluation of new macroporous
- Silicone lung
- Thin silicone permeation properties

Oximetry.

- Theory and construction of oximeters
- Photometer for SO2
- Analog computer for ear
- Polarographic method for oxygen content
- ___
- Comparison of ___ and angiocardiography
- Apparatus for rapid oxygen content measurement
- Colorimetric method for oxygen content
- Dual wavelength reflectance
- ___ in vivo with a cyclops instrument
- ___

Lyman (2) 1973
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- Fibre optic __ Effect of pH and hematocrit
- __ An improved system
- __ Present and future applications
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- Light adsorbing and scattering properties of blood
- On-line respiratory gas monitoring
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- Determination of oxygen saturation of blood
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Oxygen.

- Control of __ saturation during extracorporeal circulation
  __ dynamics in static membrane oxygenation
  Fibre optic catheter for measurement of P02
- Oxygenation in femoral bypass.

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- " (2) 1972
- " (3) 1971
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- Philips (1) 1970
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- Mook (1) 1968
- Philips (1) 1970
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- Ishikawa (1) 1973
- Anderson (1) 1967
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- Blumenfeld (1) 1973
- Clerbaux (1) 1973
- Gordy (1) 1957
- Johnson (4) 1970
- Kramer (1) 1951
- Loewinger (1) -
- Lepeshkin (4) 1932
- Earle (1) 1926
- Gomes (1) 1972
- Santiago (1) 1973
- Wiedermeier (4) 1971
- Roshe (1) 1973
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\[ x \] pH and pCO2 in capillary blood  
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\[ x \] Response of ___ to pH induced changes  
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Severinghaus (1) 1953  
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Peirce (17) 1969
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Chopra (1) 1973

Perfusion.

Pulmonary lesions produced by ____
Simple ____ apparatus for lung fix

Schramel (2) -
Brody (1) -

Plastics.

Application of ____ to membrane oxygenation

Galletti (5) 1970

Platelet.

Kinetics
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kineatics
Role of ____ dialysis membrane in thrombosis
Emerging concepts of ____ function
____ emboli in oxygenators and filters

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Priming.

Frozen blood for oxygenator priming

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Structural effects at blood-gas interfaces

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- Interaction of ___ protein with membrane
- Surface adhesion, deformation and attachment
- Mechanics of low oxygen affinity in the ___
- Intraerythrocytic regulation of blood oxygen ___ metabolism and methemoglobinemia

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- Kusserow (3) 1968
- Melrose (3) 1971
- Scala (1) 1969
- McCaughan (2) 1960
- Cahill (1) 1956
- Cappelletti (1) 1961
- Koller (1) 1967
- Lundé (13) 1967
- Osborn (4) 1955
- Salisbury (1) 1955
- Nara (1) 1971
- Frantz (1) 1963
- Bellhouse (1) 1973
- Agarwal (1) 1973
- Shohet (1) 1972
- Sinet (1) 1972
- Blackshear (8) 1972
- May (1) 1972
- Garby (1) 1972
- Harris, J. (1) -
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Recent advances in the field of ____ structure
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Baker (1) -
Oelschegel (1) 1973
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Day (2) 1964

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- Kylestra (1) 1961
- Peirce (5) 1960
- Gayford (1) 1973
- Effler (1) 1956
- Chopra (1) 1973
- Lautier (4) 1973
- Röver (1) 1973
- Katsuhara(1) 1968
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- Gaylor: (3) 1973
- Lindsay (1) 1973
- Althaus (1) 1973
- Valitov (1) 1973
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