Progress in Membrane Oxygenator Design

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Clinical application of a membrane lung was first reported in 1958, by Cloves and Neville. Its potential advantages over existing direct gas-contacting devices such as screen, film, and bubble oxygenators were recognized immediately. During the 15 years since then, many advances in both fabrication technology and techniques of use have brought the membrane oxygenator closer to being a fully practical tool with broad acceptance. The purpose of this review is to trace the development of the various classes of membrane lung, to consider the major proven and potential applications, especially those for which no alternatives are foreseen, and to review the current status and the obstacles still to be overcome.

The history of extracorporeal circulation has been presented in works which are both invaluable references and fascinating histories of scientific endeavor. Outstanding among these is the monograph by Galletti and Brecher, in which many of the problems still facing us today were first presented.

To put the membrane lung into perspective, it may be useful to cite certain milestones in oxygenator development. In 1812, Le Gallois demonstrated the viability of isolated tissue perfused by blood, and proposed that a pump providing arterialized blood should be able to maintain life indefinitely. The techniques of debridement and the use of citrate were discovered during the nineteenth century, and by 1900, several oxygenators had been devised which could be used to perfuse and maintain isolated organs. A major turning point came with the introduction of heparin by McLean in 1916, enabling the experiments to progress from the single organ to the whole animal. Gibbon's report, in 1937, of the first cardiopulmonary bypass during a period of total pulmonary-artery occlusion, provided the major modern impetus to oxygenator development, which, after World War II, proceeded rapidly. By the early 1950's, several groups had tried mechanical oxygenators and, although Dogliotti, Dennis, and others had begun clinical use of oxygenators, it seems entirely fitting that the pioneer in modern oxygenator development, Dr. John H. Gibbon, Jr., was the first to use a mechanical lung successfully for total cardiopulmonary bypass during surgery. During this period, many varieties of oxygenators were devised and examined, but those proving most successful have been the rotating-disc devices and several of the disposable bubble oxygenators.

The major problems associated with the use of the early heart-lung machines were recognized to involve trauma to the blood: protein denaturation, destruction of erythrocytes and platelets, and embolization of gas, thrombi, and antifoam particles. These problems, due largely to the direct exposure of the blood to gas, were the stimulus for the development of membrane lungs.

The original observation of gas exchange through a synthetic membrane is attributed to Kolff, who in 1944, with Berk, observed arterIALIZATION OF THE BLOOD AS IT PASSED THROUGH THE CELLOPHANE CHAMBERS OF THE FIRST ARTIFICIAL KIDNEY. The first true oxygenator was described 11 years later by Kolff and Balzer, who used their device successfully in experimental animal perfusions. Encouraged by these investigations, Cloves and his co-workers began work on experimental oxygenators, and in 1958, Cloves and Neville reported the first clinical applications of a membrane lung, with a successful series of cardiac operations, as well as two attempted cardiopulmonary resuscitations.

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After this demonstration that a patient could be adequately supported with an oxygenator in which the blood-gas contact was entirely eliminated, many groups launched development projects, but progress on membrane oxygenators was slow, because the devices were unreliable and cumbersome (Clowes' first clinical oxygenator required 25 m² total membrane area to support an adult) and could not compete with gas-contacting oxygenators for short-term use.

Work on membrane oxygenators has continued, however, because, as in all areas of surgery, the use of an existing device with recognized shortcomings is justifiable only until there is a better alternative. Today the membrane lung has progressed from the original design of Clowes to several working systems in routine clinical use and others in the advanced stages of testing.†

Problems in Membrane Oxygenator Development: An Overview

There are two general classes of problems in the design and use of membrane oxygenators for which satisfactory solutions are still being sought: 1) the interaction of blood with foreign surfaces and 2) the engineering design of systems to carry out gas transfer with this complex and fragile fluid. To a large extent, work in these two broad areas has been carried out independently, and it is only in very recent years that progress in either has been sufficient to begin to join them effectively. Surface interaction is the most fundamental problem because it is the basis of all the complications of clotting and blood trauma produced when blood is in contact with any material other than its native endothelium.§

Elimination of direct exposure to gas and better selection of pump and tube materials have greatly reduced the grosser aspects of blood trauma, but these improvements have done little for the problems of thrombosis. Thrombus formation in the oxygenator not only presents the obvious direct hazards to the patient of embolization and possible consumption of platelets and coagulation proteins, but also can greatly reduce the functional gas-transfer area.²⁶ The wide variety of thromboresistant surfaces developed and tested has recently been reviewed by Cott and Furuse.⁶⁶ These materials, together with newer substances which will undoubtedly be introduced, will do much to extend the applicability of artificial organs. At present, however, there is no synthetic surface which is truly nonthrombogenic, nor is it even clear what the properties of the ideal material should be.

Progress in this area has been reviewed by Salzman,¹²⁰-¹²² who points out that inadequacies in materials currently available cannot be expected to be overcome without significant increase in our understanding of the physical chemistry of blood-surface interactions.

For the present, artificial organs will have to be designed and used with the recognition of the hazards of coagulation and platelet deposition. These hazards can be reduced, but not eliminated, by careful selection of surface materials,¹⁰⁶,¹²⁹ some of which can be pretreated with various substances such as albumin to render them less active.¹⁰⁹,¹¹¹,¹²⁷,¹³⁰ The degree to which thrombosis can be prevented by pharmacologic agents is not clear. Anticoagulation with materials such as heparin blocks fibrin formation but does not reduce platelet activity, which could be equally limiting in the prolonged use of an artificial organ.¶

Platelet adhesiveness and the release reaction inducing platelet aggregation can be controlled to some extent with the dextrans, aspirin, antihistamines, and other agents.¹²⁸,¹²⁹ Before these measures can be developed and used with safety, however, more information about

† The scope of oxygenator studies initiated within the past several years has broadened to include new types of membrane systems, as well as devices in which the membrane is eliminated and the blood is contacted with an inert, immiscible, carrier fluid such as a fluorocarbon.¹⁻³⁰

§ The proceedings of a conference on Mechanical Surface and Gas Layer Effects on Moving Blood have recently been published as a Symposium,³² which contains several of the papers cited in this review.

¶ There is evidence that heparin, in solution or bonded to a surface, increases platelet adhesiveness, but in the case of heparinized surfaces, this tendency can be reversed by albumin pretreatment.¹³⁰
the ability of the body to tolerate simultaneous inhibition of the two primary hemostatic mechanisms over prolonged periods of time is needed. Also, although the action of heparin can be blocked with protamine, there are no known antidotes for the platelet inhibitors, making this aspect of hemostatic control more difficult and hazardous. The concept of regional heparinization of the external organ to allow normal clotting mechanisms in the patient during prolonged perfusion has not yet proven workable because of the high blood flow rates involved and the lack of rapid methods of titration necessary for regulation of the system.

The second major problem, engineering design, is closely tied to the difficulties of blood-surface interaction, because it is essential to know which are the most suitable materials for construction; an actively thrombogenic material, for example, would be ruled out for use in a membrane oxygenator no matter how favorable its gas-transfer properties might be. It is an unusual piece of good fortune (nature rarely makes such gifts) that the silicones, first attractive medically because of their relative inertness, have proved to have by far the greatest permeability to both oxygen and carbon dioxide of any known synthetic polymer, making silicone rubber the material of choice for most membrane lungs.

The thromboresistance of a given material, and the conditions under which the various types of thrombus will develop in a flow system, are strongly dependent on hydrodynamic design. For example, in zones where the blood is moving slowly, red thrombi with a fibrin matrix are found, whereas platelet deposition is usually the primary clotting event in zones of high velocity, particularly where a stagnation point exists, as at a flow bifurcation. These phenomena are strikingly manifested in membrane oxygenators, with their large surface areas and complex hydraulic geometries.

In spite of the unsolved problems of thrombosis, considerable progress has been made in the understanding of the basic gas-exchange function of oxygenators and the application of this knowledge to the development of practical and reliable systems. As membrane devices with greatly increased gas-transfer efficiencies have been developed, it has been necessary to create new models for oxygen uptake and CO₂ elimination to describe mechanisms that have not been relevant to the physiologist concerned with natural functions of respiration. To cover the range of studies in this area would enlarge this review to an unmanageable scope. The interested reader is referred to recent symposia dealing with basic and applied aspects of blood oxygenation; in addition to the papers included in those collections, a selection of articles will also be helpful. 

Clinical Applications

Two general classes of application are foreseen for membrane lungs. They can best be considered separately, because the objectives are different and they present quite different technical problems: 1) to replace the existing gas-contacting oxygenators for use in routine cardiac surgery, and 2) to provide periods of prolonged extracorporeal support, lasting days or possibly weeks, for patients with acute, but potentially reversible, respiratory or cardiac failure. The latter should lead to a third type of application, directed at the support of acutely ill patients long enough to restore them to a condition permitting definitive intervention. To consider but two examples: veno-arterial bypass of patients in cardiogenic shock prior to, and during, myocardial revascularization; extracorporeal support of patients with cystic fibrosis, who, during acute crises, could be helped by pulmonary lavage. These two examples seem especially attractive and plausible, because in neither case would a period of extracorporeal support, in and of itself, be expected to produce significant or lasting improvement.

For short-term surgical use of an oxygenator, the problems are well defined, based on 20 years' experience with gas-contacting devices which have proven adequate in most applications. The most stringent limitation on current techniques is that imposed by time. Although most cardiac operations can be completed within the safe 1-2 hour period, there are occasions when greater latitude to extend the time on bypass can be a decisive factor.
These include unforeseen intraoperative complications and cases of extended resuscitation of patients who cannot be taken off the pump.\(^{19, 62}\)

Neonatal cardiac surgery represents one area in which oxygenators have had no impact; open-heart operations on newborn infants using gas-contacting oxygenators has proven so unsuccessful that current methods of treatment generally involve early palliative measures without bypass, followed by a further complete operation at some age past six months. Deep hypothermia with circulatory arrest\(^{26}\) has been applied for conditions which formerly were untreatable, but these procedures have been more successful in older infants and are still limited in time. Membrane lungs have been used in attempts to treat neonatal respiratory distress\(^{45, 141}\) and, recently, during surgical procedures in older infants.\(^{78}\) Should new membrane systems currently under development for neonatal surgery\(^{29}\) prove successful, they could be of great value in this application.

Even for the surgical procedures in which the gas-contacting heart-lung machines are now used successfully, and are consequently well entrenched, it would be short-sighted not to consider a place for a better oxygenator; but in this case “better” implies improvement in at least three respects if significant changes in surgical practice and industrial manufacture are to occur: reliability and ease of use, cost, and most important, improved patient survival and/or lowered complication rate. For this application thromboreistance is not a primary criterion, because not only is heparinization necessary during periods when the heart is open, it presents no great threat under the controlled conditions of the operating room. Progress in usability and cost has been encouraging within recent years, but if the comparison were limited to these aspects alone, a membrane lung might never be competitive with a device as inexpensive and simple as a disposable bubble oxygenator.\(^{122}\) “As good as” will not be good enough. Therefore, the third question may well be decisive, and it is this area in which data are lacking.

The first practical membrane system, the Bramson lung,\(^{14}\) has been in routine use in surgery since 1965,\(^{62}\) and the Landé-Edwards oxygenator, since 1969.\(^{19, 29}\) In spite of this considerable experience with two membrane devices used for short-term cardiopulmonary bypass, by groups who are also using gas-contacting oxygenators, it has not yet been possible to demonstrate objectively, with a controlled study, any differences in mortality or morbidity attributable to the oxygenator used during routine uncomplicated cardiac operations.\(^{76, 88}\) Rather, such evidence as there is favoring the membrane lung is largely anecdotal, and is based on clinical impressions, with enthusiasts and detractors in both camps. It is possible that the vast majority of patients can tolerate the insults of blood trauma, and that in the long run, various aspects of surgical technique, such as operative speed, the degree of tissue trauma, and proper use of coronary perfusion and suction, are far more important than the particular types of supporting hardware used. It is also likely that the indices used thus far to determine injury or complication are not sufficiently sensitive. In 1967, Burns\(^{140}\) showed that cellular enzymes released from specific organs, such as the liver and heart, could increase immediately following a two-hour perfusion; these changes were quantitative and predicted hepatic and renal complications which were not even evident for two to three days after the perfusion. As oxygenators are used for longer periods during extended surgical procedures, it is clear that new approaches which could provide better assessment of equipment and methods, such as Burns’ isoenzyme technique, will have to be tested. Also under investigation are neurologic and psychologic indices to be used during a long postoperative follow-up period.\(^{88}\)

For the application of membrane oxygenators to long-term bypass, the problems are quite different. While free-surface oxygenators proved to be wholly unsuited for any perfusion exceeding a few hours,\(^{27, 92, 95, 132}\) many groups have shown the ability of experimental animals to tolerate prolonged periods of extracorporeal bypass with membrane oxygenators.\(^{5, 42, 57, 67, 92, 94, 95, 115, 142}\) Even in the healthy experimental animal, however—and in all the investigations cited, it has usually been possible to restore the animal to good health.
in the days following bypass—prolonged extracorporeal oxygenation involves considerable stress and risk. When the various data are all boiled down and compared, and the recurring euphemisms decoded ("no pathologic changes directly attributable to the oxygenator"), it becomes clear that sepsis is an ever-present threat, and that our attempts to walk the tightrope between thrombosis and hemorrhage are primitive and inadequate. The experience in all laboratories indicates that both hazards increase with the duration of bypass. Although sepsis might at first seem largely preventable with adequate technique, there is evidence of reduced phagocytic activity following perfusion, and it is possible that exposure of blood to extracorporeal devices can in some way impair the body's normal immunologic defenses. Whether the dangers of systemic anticoagulation increase with time for biologic reasons—platelet counts do decrease during perfusion, and their function could be impaired to the point that hemostasis fails—or whether the length of time on bypass simply increases the odds for technical error is not clear, but the problem is one shared by all investigators. One of the major reasons that the artificial kidney has proven practical for chronic dialysis is that the patient is allowed several days of respite between sessions. The artificial lung, however, could offer little therapeutic value as a part-time organ.

The very concept of applying an oxygenator for prolonged support is fundamentally different from its use in surgery; the machine itself is assigned an essential therapeutic role, the major objective being to buy time for the body's restorative processes to work. It is this element of time required on bypass that has made the concept so difficult to test. Any healing which might occur can be negated or obscured by the lethal side-effects of the procedure. After 72 hours of continuous perfusion in an experimental animal, or a patient, how can it be determined whether deterioration is an inevitable result of the original lesion or is iatrogenic?

Nonetheless, experience in experimental-animal perfusion has been sufficiently encouraging to justify clinical trials in patients in whose cases there is unequivocal failure of established modes of support. Among the conditions for which prolonged extracorporeal support has been attempted are: neonatal respiratory distress syndrome 45, 114; acute respiratory failure from conditions such as pneumonia, aspiration pneumonitis, and posttraumatic pulmonary insufficiency 71, 114; myocardial failure and cardiogenic shock. 59, 99

In the latter category, Landé has reported temporary survival, for as long as 20 days, of patients who eventually succumbed to their preexisting coronary-artery disease 96; this would certainly appear to be a group to whom prolonged support followed by corrective surgery could offer real hope. 109

In the treatment of respiratory insufficiency, the potential for success is less well defined. Barring the future feasibility of lung transplantation, surgical procedures do not offer significant promise, and success will depend on the ability of the lung to heal before it and other organs or organ systems can collapse from the stresses of the bypass procedure.

The experiences of Hill and associates 50, 71 with the Bramson oxygenator, 14 and those of Zapol 114 with the Kolobow spiral-membrane lung 51, 52 suggest that the likelihood of reversing a pulmonary lesion is greater in the inflammatory exudative phases than in the consolidating fibrosing lung with parenchymal damage. While this difference is undoubtedly related to the disease process itself, it must also depend on the timing of the start of bypass and on the events occurring during the early stages of treatment. Hill has suggested that in many cases time alone may not be sufficient, and that means are needed to improve the milieu of the tissues of the lung for healing to occur. 71 Clearly, there is a pressing need for more sensitive diagnostic and predictive techniques by which patients who need extracorporeal support can be singled out early. Early application of an oxygenator with adequate perfusion will not only arrest the disease sooner, it will eliminate much of the progressive pulmonary injury caused by prolonged mechanical ventilation with high concentrations of oxygen and excessive airway pressures.

Recently, Hill and associates 79 reported survival and full recovery of a patient following 75 hours on veno-arterial bypass. The patient
was a young man who went into acute pulmonary insufficiency several days after sustaining massive trauma in a motor vehicle accident. In their earlier experiences with clinical perfusions, Hill\(^{71}\) and Zapol\(^{111}\) saw frequent evidence of improvement in pulmonary function, but in all cases lethal complications, usually hemorrhage or sepsis, intervened. This first survival is both significant and encouraging; with adequate techniques, and in at least certain patients, time can be bought and impaired pulmonary function can be restored with extracorporeal support.

Further progress will undoubtedly be achieved with increased clinical experience which is entirely justified in potentially salvageable patients who would otherwise die. A supportive area of investigation which could be of great value would be the development of animal models of acute pulmonary insufficiency. Up to the present time, most of the experimental oxygenator studies have been with normal animals, in some cases rendered hypoxic by breathing reduced oxygen mixtures. These studies are useful in demonstrating tolerance to the procedure, and can cast light on some of the physiologic aspects of extracorporeal support, but they cannot contribute to our understanding of the efficacy of the procedure in reversing disease. Among the disease models studied, oleic acid injected intravenously in the dog has been tested,\(^{2,7,29}\) but it does not appear to produce lesions which respond in the same way as those seen in man. More promising may be the hemorrhagic-shock model produced in the pig by Lowery et al.,\(^{55}\) which might profitably be examined in other animals, such as the sheep, as well. Predictable and reproducible experimental models would contribute to the development of the early and sensitive diagnostic techniques which are so sorely needed, and it may be in this area that they will have their greatest value.

Membrane Oxygenator Designs

**Membrane Materials**

As is evident in the following discussion, progress in the development of membrane lungs has been closely linked to the availability of suitable materials. Therefore, a brief chronology of membrane development is helpful in tracing the evolution of the different types of oxygenators.

When Clowes was searching for the most suitable membrane, he compared the various materials available, and found that ethylecellulose and polyethylene were the most permeable to oxygen and CO\(_2\).\(^{22}\) Although ethylecellulose gave somewhat greater gas transfer, the better mechanical properties of polyethylene led to its use in the clinical oxygenator. In his 1958 report,\(^{24}\) Clowes mentioned that teflon had become available, and, although it showed even greater gas permeability, he continued to work with polyethylene because the new material was both fragile and expensive. By the late 1950's, manufacturing techniques had improved, and teflon received the widest use between then and the mid-1960's.

The silicones were first introduced in the late 1940's, but it was not until 1957 that Kammermeyer\(^{14}\) reported the very high permeability of the dimethyl silicone elastomer to O\(_2\) and CO\(_2\). Subsequent investigations have shown that the permeability of silicone rubber for oxygen is more than 40 times that of teflon.\(^{59,61}\) Silicone is also unique among synthetic polymers in its selectivity; the ratio of CO\(_2\) to O\(_2\) permeability is in the range 5 to 6, whereas in most other materials that have been tested as membranes, it is of the order of 2.\(^{17,59,61}\)

The high permeability of silicone, together with its selective property tending to enhance CO\(_2\) transfer, made its application to the membrane lung attractive, but early efforts to produce thin membrane yielded materials of uneven quality and low mechanical strength which could not be used with confidence in an oxygenator. Galletti and Brecher\(^{59}\) credit Thomas\(^{132}\) with producing the first silicone membrane by dip-coating a nylon mesh; in 1962, Marx et al.\(^{132}\) used a similar technique to make membranes for their experimental oxygenator. Improvements in silicone sheet membrane were slow to come, although by the mid 1960's several companies were producing silicone film for use in experimental oxygena-
tors by processes such as dip-coating, batch-casting, and, more recently, calendering. The development of adequate extrusion processes led to the manufacture of thin-walled tubes, and in 1963, Bodell et al. described the first silicone capillary oxygenator. In the meantime, efforts were also directed at the development of copolymers of silicone with other materials as a means of improving the quality and strength of the membranes.

In 1969, Burns described a new process, developed at Hammersmith Hospital, London, for low-cost production of silicone membranes of greatly increased strength, which were thinner than those produced by other processes, and virtually free of pin-holes. The improved properties of the Hammersmith membrane appear to be due primarily to careful control of the various chemical steps, especially catalysis and curing, and to the fabrication process itself, which involves continuous solvent-casting onto a moving substrate.

Even with these various advances, however, polymer technology as applied to membrane development is still in its early stages. In addition to needed improvements in surface compatibility with blood, it is likely that there is much that can be done with the basic chemistry of silicones, and possibly new untested polymers, to lower their cost and to improve their properties of strength and gas permeability further.

**Design Concepts**

The basic physical processes which describe the operation of the lung—or of any organ or artificial device for mass transfer—are convection, or bulk transport of the fluids, in this case blood and air, to the exchange sites, and diffusion, the actual process of exchange that occurs at a membrane or capillary interface. The structure of the natural lung is such that these processes are well matched because of the small diameter of the capillary (10 μm) and the large composite surface area for gas exchange (70 m²). In artificial organs the major latitude for improving performance by design techniques is in the convection process, diffusion being fixed by the properties of the conveying and diffusing substances, and by the concentration gradients.

A gas-contacting oxygenator is extremely efficient because of the high degree of convection, transporting the blood to the diffusion interface, and the elimination of the alveolar membrane, which imposes a finite, although small, diffusion resistance. The interposition of a membrane between the blood and gas phases in an oxygenator produces two transfer-limiting effects whose relative magnitudes depend on the membrane material and on the hydraulic design of the system: first, the resistance of the membrane itself; and second, an additional diffusion resistance within the blood. Adjacent to the membrane there exists a slowly-moving boundary layer which impedes convection of the blood to the exchange surface. In natural capillaries the boundary-layer diffusion resistance is small because of their small size. Man, however, is unable to compete with nature as an architect; the smallest passages yet made through synthetic materials which have a reasonable likelihood of remaining patent are of the order of 100 to 500 μm. Because the time needed to oxygenate a film of blood varies as the square of its thickness, these relatively large passages are extremely inefficient as diffusion sites. Therefore, the development of highly permeable synthetic membranes solved only part of the problem, and it is the blood diffusion resistance which imposes the major limitation on the gas-transfer performance of artificial membrane lungs. Blocked by our inability to reproduce the natural capillary to scale in the membrane lung, the only solution is to modify the structure of the boundary layer by creating lateral mixing within the blood passages—in other words, make better use of convection to facilitate diffusion.

Most of the membrane oxygenators under investigation today incorporate design features which, by passive and/or active means, promote internal mixing to augment gas transfer. As examples of passive schemes: remixing of the blood as it passes sequentially through sets of short passages, creation of membrane-surface irregularities by the support structure; insertion of screens or surface elements into the blood passages; and incorporation of curved passages to produce secondary flows. Active mixing designs include periodic pulsa-
tion or agitation of the membrane chambers and externally-induced secondary flows.

The effectiveness of these design techniques and the extent to which membrane oxygenator performance can be improved by convective mixing depend on several factors:

First, the intensity of mixing which can be induced by passive means in narrow blood passages is limited, because the passages themselves have a strong stabilizing influence on the flow. This damping effect is more pronounced when mixing depends on eddies produced by screens or surface irregularities than for systems in which there is a regular pattern of secondary flows, as in a coiled tube.††

Second, to substitute for the lungs, an oxygenator must be capable of transferring essentially equal amounts of oxygen and CO₂. The disparity in diffusion gradients which can exist under physiologic conditions would appear to favor oxygen uptake, inasmuch as a P₂ difference of 650–700 mm Hg can easily be established across the membrane, whereas the venous P₃O₂ at most cannot exceed 60–70 mm Hg. However, the actual relative transfer rates of the two gases which can be achieved depend on their respective permeabilities in both blood and the membrane. In plasma and other aqueous materials, such as the alveolar-capillary membrane, the higher solubility of CO₂ results in a twentyfold greater permeability, and accordingly, both the natural lung and gas-contacting oxygenators have greater capacities for CO₂ elimination than for O₂ uptake. Similarly, in those membrane lungs in which the major transfer resistance is in the blood phase, O₂ exchange is limiting. On the other hand, with efficient convective mixing, CO₂ transfer becomes severely limited by the silicone membrane resistance and, with an oxygenator operating at the membrane limit, can reach only approximately half the oxygen-uptake rate.††

Finally, if it were possible to construct an oxygenator with membranes of truly negligible resistance, and to induce any desired degree of convective mixing, an ultimate diffusion resistance, that imposed by the finite size of the erythrocyte, would be encountered. Rough-
ton and Mochizuki have shown that while the oxygenation of hemoglobin is extremely rapid, the erythrocyte takes about 0.2 sec to become saturated because of the time necessary for the oxygen molecules to diffuse into the interior of the cell. From the practical standpoint, it may never be possible to observe this limitation in an oxygenator, because hemolysis could intervene before convective mixing of sufficient intensity was reached. The significance of the erythrocyte diffusion resistance is that it would impose a lower limit on exposure time of the blood to the exchange membrane, and thus an upper limit on the blood flow rate for a given membrane area. A simplified model of this condition was advanced by Kopf, based on experiments in an oxygenator with mechanically-induced secondary flows, operating at gas transfer rates below the capacity of the 2-ml (50-µm) silicone membrane.

Clowes' first oxygenator was the prototype of the sandwich design, in which closely opposed pairs of membrane sheets conduct the blood between alternating oxygen spaces. Although this design is inherently diffusion-limited, from a practical standpoint it represents the simplest approach to putting a lung in a box; the structural components are identical, and, with proper manifolding, modules can be stacked to give any desired gas-transfer capacity (fig. 1). Most of the early membrane systems represented elaborations of the basic Clowes approach, and of the membrane oxygenators in clinical use today, three—the Bramson, G.E.—Peirce, and Landé–Edwards—are essentially of this type, although, as discussed below, there are certain structural and functional differences.

In his early studies, Clowes found it difficult to establish a uniform planar flow between flat membranes; the blood tended to collect unpredictably in thick rivulets. Therefore, he supported the membranes between pairs of grooved plates, creating, from the functional standpoint, a system of straight capillaries manifolded in parallel. In the Landé–Edwards oxygenator, which is similar in design to an earlier configuration proposed by Esmond, this principle has been exploited to
give an extremely compact unit suitable for mass production (fig. 2).

When teflon and silicone rubber were first used, they were supported by fabric screens, and it became evident that surface irregularities could produce some local mixing through the formation of small eddies. Kolobow conceived of the idea of deliberately deforming the membrane, by forcing it to penetrate through the screen to give surface irregularities as well as a larger transfer area. He also introduced the concept of lowering the pressure on the oxygen side of the membrane to eliminate the very real hazard of gas embolization following any accidental membrane rupture. As discussed below, this design can also result in some active mixing. Topologically, Kolobow's spiral-membrane lung (Sci-Med, Inc.) might be considered a rolled-up sandwich oxygenator; a long flat membrane tube, or envelope, containing a woven plastic spacer screen is wrapped around a central cylinder (fig. 3). Oxygen passes through this tube, and the blood flows parallel to the axis of the cylinder between the folds of the membrane.

The Bramson lung (Cutter Laboratories, Inc.) is also of the basic sandwich type, but with mixing induced by screens in the blood passages, a method used earlier by Marx. Bramson incorporated thermal regulation into the oxygenator by the use of water-filled bladders between each circular pair of membranes. The water bladders are connected to an external heat-exchange system; they also serve as shims to maintain the constant membrane spacing set by the blood screens. Screens between the water bladders and the adjacent membranes provide the space for oxygen to flush the membrane surface (fig. 4). Although
the blood screens improve the gas-transfer efficiency of the Bramson lung, their spacing function is equally important in contributing to the overall reliability of the system.

Peirce introduced the concept of incorporating regularly-spaced protuberances into the membrane to act in the same way as a screen in maintaining a blood space of uniform thickness. His multiple-support system behaves much like a screen to induce a certain amount of mixing, primarily by forcing the blood to follow tortuous paths, with continual remixing of the individual streams. Peirce found the improved operation more than offset the loss of active membrane area at the support points. This method of fabrication, originally proposed by Bluemle for dialysis membranes, has been adopted in the G.E.—Peirce copolymer membrane lung.

The use of tubular capillaries, instead of stacks of flat membranes, first explored by Bodell et al. offers the advantage that the dimensions of the oxygen and blood compartments can be better controlled. Capillary oxygenators have been operated both with oxygen flowing in the capillaries and blood in the surrounding space and, in the inverse configuration, with blood in the tubes and the
oxygen flushing the exterior surface of the capillary bundle (fig. 5). The latter approach, first demonstrated by Wilson et al.,142 has proven the more successful and has been followed in most of the recent development studies of capillary, or hollow-fiber, devices.15, 20, 41, 50, 123 Practical drawbacks still to be overcome include thrombus formation originating in the manifold or header chambers26, 55 and the cost of materials, which is still higher than that of sheet membranes of equivalent gas-transfer capacity. Capillary oxygenators appear relatively simple to manufacture, they lend themselves to compact design, and with further progress should become competitive with other systems.

Among the various passive mixing schemes applied to membrane oxygenator design, the most efficient in its simplicity, and probably the most efficient, is the coiled tube (fig. 6), originally investigated by Weissman and Mockros129 and successfully developed by Dorson and his co-workers into a working oxygenator which is undergoing clinical trials.40, 42 When a fluid flows through a curved conduit, the imbalance of centrifugal forces between the points in the boundary layer and those in the center of the tube creates a pair of counterclockwise vortices, or spiral flows, which continually sweep the fluid away from the wall, replacing it from the central part of the stream.†† 45, 119, 120 This principle has long been employed as a method of reducing thermal film resistance in coiled-tube heat exchangers,162 and its analogous application to gas-transfer devices is intuitively reasonable. Dorson42 showed a more-than-twofold increase in $O_2$ transfer with coiled capillaries, over an equivalent array of straight tubes. Because of the convective mixing, the tube diameters can be somewhat larger than those of the straight capillaries, making them less subject to plugging. In addition to being compact, the coiled-tube configuration eliminates the necessity for obstructions in the blood passages which can initiate thrombus formation.

Active means to induce mixing in the blood appear to have been under investigation at least as early as the work of Kolobow,81 who used a cycling pressure in the oxygen passage of the spiral-membrane lung to produce mi-

†† As a note of historical interest, this phenomenon was first explained in 1876, by James Thompson128 in his description of the flow structure in river bends, in which the secondary motion consists of a single spiral because of the frictionless free surface. This helicoidal motion is largely responsible for the patterns of erosion and deposition in curving rivers and, as indicated in many of Mark Twain's writings, was familiar to river-boat pilots.
progress in membrane oxygenator design

Fig. 5. Schematic view of the Dow hollow fiber oxygenator which is typical of the configurations used in capillary lungs. The capillaries are assembled in a bundle around the oxygen-distribution manifold. The tube sheets are formed by potting the ends of the capillary bundle in a material such as RTV silicone; the molded bundle is cut off squarely at the header face (by permission).

cyoscopic foci of mixing by periodic deformation of the membrane through the open spaces in the support screen. Other attempts to agitate the blood film periodically have included pneumatic pulsation of the entire membrane surface,\textsuperscript{21} massaging the surface with a moving rod,\textsuperscript{24} and rocking the entire membrane envelope.\textsuperscript{25, 26} All of the latter approaches produced only modest increases in gas-transfer performance, and it became evident how difficult it is to modify the structure of the boundary layer significantly by externally-applied mechanical forces. In addition, problems of membrane leakage and unpredictable performance have prevented acceptance of these devices.

In 1967, Illick et al.\textsuperscript{23} described a radical approach to boundary-layer modification, and for the first time demonstrated that membrane-limited transfer could be achieved in an oxy-

Fig. 6. Coiled-tube configuration with secondary flow pattern produced by the tube curvature. Application to capillary oxygenator design described in text (after Weissman and Mockros).\textsuperscript{27}

Fig. 7. The toroidal-flow oxygenator. Left, secondary flows in a rotationally oscillating torus. Compare with figure 6. (By permission) Right, schematic diagram of the membrane and support-plate configuration. The upper and lower plates are held together by an air shim (not shown) to give the system of flows through sequential toroidal chambers, as shown in the plan view (by permission).
genator. Using a rapidly spinning disc with a supported 5-mil (125 μm) silicone membrane, the disc being wholly enclosed in the blood chamber, the authors showed that oxygen transfer increased linearly with rotation speed. The maximum achieved was actually somewhat in excess of the 200 ml/m²/min capacity predicted for that membrane, possibly due to local distention or deformation of the silicone. The authors ascribe the high transfers to fluid shear caused by the disc rotation. A spinning disc induces strong secondary flows directed radially outward at the moving surface, and it is likely that this secondary motion was more important in inducing convection than simple planar shear. Unfortunately, efforts to scale this device up to a usable size were not successful because of the large amount of heat generated by the disc friction. However, the experiment was both novel and significant because it demonstrated that actively induced convective mixing reduces the blood diffusion resistance far more effectively than any passive means yet conceived can be achieved.

In 1969, Drinker et al. described the method of mechanically inducing secondary flows by rotational oscillation of toroidal membrane chambers, which resulted in gas-transfer rates nearly as great as those obtained with the rotating disc, but without its problems of heat generation and blood trauma. Their initial oxygenator was made using 10-foot lengths of 3\textsuperscript{1/4}-inch diameter 3-mil wall silicone tubing, connected to form a single endless loop or torus, with inlet and outlet ports at diametrically opposite points; the tubing was coiled about a perforated support drum mounted on a shaft which was driven to produce rotational, or angular, oscillation about the coil axis.

The secondary flows produced in this system, described in detail elsewhere, are similar in appearance to those in a simple coiled tube, but here the spiral motion is in the opposite direction, and it is more intense because of the greater velocity difference between the wall and the center of the tube. Efforts to improve reliability and to scale the toroidal-flow device up in size from the first small prototype were initially impeded by lack of adequate membrane materials. When Burns introduced the Hammersmith membrane, methods were developed to replace the tubular membranes with flat sheets clamped in pairs between support plates machined to give a system of interconnected toroidal passages (fig. 7). The toroidal-flow membrane oxygenator is being put through a broad range of preclinical studies, which are indicating that the device performs reliably in extended perfusions and gives oxygen-transfer rates in excess of 250 ml/m²/min. Current models being evaluated by Bartlett and the author have a membrane surface area of 0.45 m² and an oxygenator-transfer capacity of 100–125 ml/min. Further studies in collaboration with Edwards Laboratories are directed at the development of stacked preassembled membrane modules, to simplify assembly of the oxygenator.

Recently, Marx has re-examined the method of augmenting gas transfer by membrane agitation, and has demonstrated a capillary oxygenator, with an integral heat exchanger, in which a silicone oil is used to pulse the tubes hydraulically. Silicone oils have a high solubility for O₂ and CO₂, and thus can serve as the carrier fluid for both gas and heat transfer. At first appearance, it might seem that in this system the diffusion resistance on the blood side of the membrane would be reduced only at the expense of an additional resistance in the liquid surrounding the capillaries. However, oxygen-transfer rates of 200 ml/m²/min reported for this device are higher than those reported for any other capillary lung, approaching the membrane limit for the 3.5-mil (88 μm) silicone tube wall, and the concept merits further investigation.

Current Status and a Look at the Future

The foregoing discussions have dealt with the general areas of application foreseen for membrane oxygenators, and with the oxygenators themselves. The means of applying the oxygenator are the responsibility of the surgeon, and, therefore, do not fall within the province of this reviewer. However, in certain respects, the decisions on how to use the device must be considered in its design.

§§ Unpublished data.
For total bypass during intracardiac surgery, the procedures would not appear to be fundamentally different from those in use today; total diversion of the caval flows and return to the aorta via the femoral vein. For prolonged bypass, the procedures are less well established, because the applications are still under investigation. Partial support by venovenous bypass has long been an attractive concept; to the surgeon, because inflammation is simple and is confined to the venous circulation, and to the engineer, because the entire oxygenator system operates at a lower pressure. Recent studies suggest, however, that the benefits which can be achieved by venovenous bypass are limited, and that veno-arterial perfusion may offer the greater promise. If the latter course is taken, it may be necessary to use diastolic augmentation, or counterpulsation, to prevent overloading of the left ventricle, placing further demands on the equipment design. The relative hazards of embolization with venovenous vs. veno-arterial perfusion have been debated, but there are probably no grounds for distinguishing the procedures on this basis alone. It can be argued that the injured lung could poorly tolerate the additional insult caused by venovenous bypass; on the other hand, arterial embolization to a vital organ could be rapidly lethal. Whichsoever method is selected, the demands on equipment design and perfusion techniques are equally stringent.

Partial support may well prove feasible for the patient whose heart or lungs can maintain part of their normal function, but it seems clear that an oxygenator and pump, once put into service, must be able to assume the entire cardiopulmonary load. There will be no way to tell in advance the proportion of gas exchange or cardiac work that a patient will sustain during an extended period. Thus, the clinician may strive for partial support, but the engineer must not count on it.

As to the future, it is conceivable that technological advances can reach a level such that extracorporeal appurtenances will be sufficiently safe and routine that new applications for chronic disease, and even elective, nonmedical, uses of oxygenators, will become a reality. It is the feeling of this reviewer, however, that there are so many immediate problems to be overcome, for situations of urgent need, that it is more reasonable to restrict ourselves to the problems at hand for which there is a strong likelihood of success and contribution to the needs of mankind.

The discussion of membrane oxygenators summarizes those designs which have had the greatest influence on the trends of development. Some of the approaches have been proven by successful reduction to practice, while others offer the potential for major advances. The list does not include all oxygenators: to do so would have introduced unnecessary repetition, because there are variations on a limited number of themes.

It should be evident, however, that opinions about the design techniques which can come closest to achieving the necessary gas-transfer capacity, reliability, and safety needed for a satisfactory oxygenator vary widely. At the present time, membrane lungs must be considered developmental, and, although increasing, their use is still confined primarily to the centers where they originated. Until a good many different designs become widely available, and have been subjected to both systematic comparison and extensive clinical testing, assessments of their relative merits will inevitably be subjective, and biased by the enthusiastic views of the inventors.

In the meantime, our understanding of membrane oxygenators, and the physiology of extracorporeal circulation, is at the stage at which competition in the race towards a common accepted goal is needed and should be encouraged. In this, as in other problems in experimental and applied science, the best means of achieving a desired end are determined by technical obstacles. The diverse approaches to oxygenator design and analysis have just begun to give definition to these obstacles, and will contribute to their solution. Therefore, while pure duplication of effort is wasteful, alternative concepts must be investigated far enough to determine their validity and to delineate those areas where compromise must be accepted.

Lacking such definitive conclusions, it is nonetheless provocative to reflect on the criteria which are most relevant for the opti-
mization of oxygenator design. For example, should we even be concerned with gas-transfer efficiency, or can we accept the inherent diffusion limitation of the standard types of sandwich and capillary lung, with their correspondingly larger surface areas? Sufficient progress in nonthrombogenic surfaces, hydraulic design, and manufacturing technique might ultimately result in an inexpensive and reliable membrane lung, which need not be constrained by gas-transfer efficiency any more than is the natural lung. Certainly all would agree that a compact, but inefficient, oxygenator which sat quietly on the table would be preferable to one which required a complex and expensive mechanical assembly, no matter how great its efficiency and engineering appeal. For the operating room this may well prove to be a successful route. In prolonged applications, however, these designs have failed to meet the essential performance criteria, particularly in regard to hemostasis and thrombosis. The development of oxygenators with reduced membrane areas, and simplified hydraulic geometry, may allow more effective application of synthetic thromboresistant surfaces and other aspects of technology. Just as man has never built a successful ornithopter, but has surpassed birds in many aspects of flight, it is quite likely that in the lung attempts to mimic nature will not be as effective as those making more appropriate use of the available materials and techniques of engineering design.

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