PLASTIC HEARTS, MEMBRANE LUNGS, AND ARTIFICIAL KIDNEYS — THE ENGINEERING OF VITAL ORGANS

by Sheldon K. Friedlander

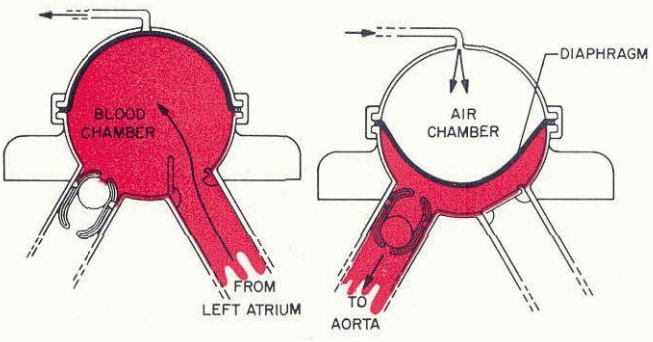
Why are engineers taking more and more interest in problems of health and medicine? In part, perhaps, it is a question of a guilty conscience. After all, engineers have seen the destructive power of their inventiveness in the effects of air and water pollution, weapons for the military, and biological and chemical warfare. Can they have as much impact, of a positive sort, in such fields as health and medicine?

While I am convinced that this is part of the story, it is necessary to ask the more general question: What makes any field of technology develop at the particular time that it does? One important factor is the state of the backup technology. For example, the rapid growth of the aircraft industry rested in part on the base of a commercially successful method for winning aluminum from its ores. A second requirement is the willingness and ability of a society to provide financial support for the development. Either mass markets, as in the case of the automobile, or military-political stimulus, as in the space program, may provide that support.

The backup technology in the form of new polymeric materials and electronic instrumentation now exists for significant advances in certain fields of medical technology. Development costs are unlikely to be supported by mass markets, and there is little doubt that the government will have to underwrite these expenses, which can be huge. While some government funds *have* been allocated to this field, they have been small in comparison with outlays for space spectaculars, military hardware, and Asian wars.

Still, progress has been made. Until recently, it has been possible to make replacements of human parts only of the most primitive types such as wooden legs and false teeth. Within the past 20 years or so, artificial hearts, kidneys, and lungs have been developed to the point where they can be used in some cases to prolong life indefinitely, in other cases to at least permit repairs during surgery. These are among the simplest of organs in their function, and it was natural to begin with them in our bioengineering efforts.

The diagram below shows an artificial heart of the type recently used by Michael DeBakey, MD, and his surgical group at Methodist Hospital in Houston. The plastic heart, about the size of a grapefruit, is activated by an air pressure mechanism which moves the diaphragm back and forth,



A schematic diagram of an artificial heart, designed to carry part of the pumping load for a period of days after a patient has undergone heart surgery. The diagram on the left shows the heart as blood is drawn in, and the one on the right as it is pumped into the aorta.

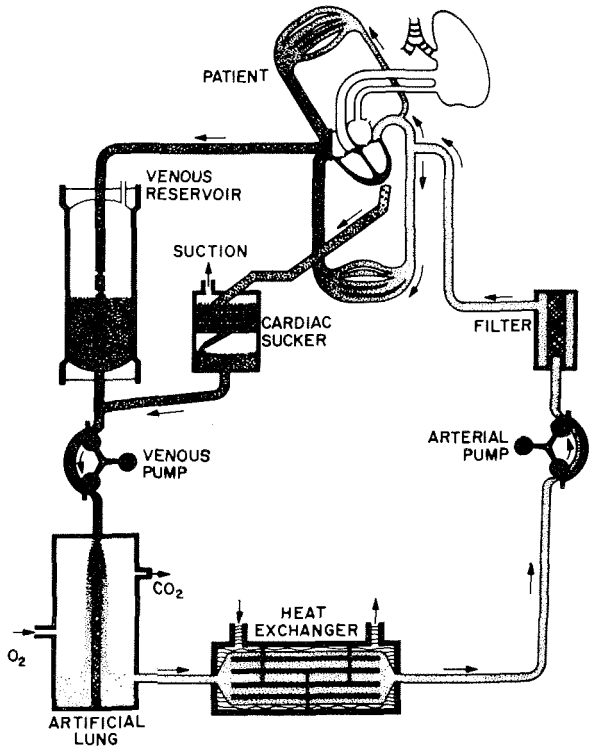
thereby producing the pumping action. Currently such devices are used for a period of days to give the patient's heart a partial holiday during and after surgery.

In a commercial artificial kidney, blood flows along one side of a membrane, and a salt solution on the other. When kidney function is impaired, this device can be used to remove potassium ions as well as urea, creatinine, uric acid, and a variety of

other toxic products of metabolism normally removed by the healthy kidney. The separation in this way of smaller molecules from larger ones is known as dialysis.

The artificial kidney was first used successfully with human patients in 1945. Current treatment with these large devices is expensive and time consuming, and the number of trained personnel qualified to operate them is small. First-year costs of treatment have been estimated to be about $20,000 per patient. Each year 90,000 people die of chronic kidney failure, and of this number at least some fraction could be saved by treatment with the artificial kidney. Only a limited number of patients can be treated with the facilities available, and the problem of selecting those who will live has been discussed at length in the popular press and on TV.

Shown below is an external circulatory system of the type used during heart surgery. It demonstrates rather clearly the characteristics of systems which engineers are accustomed to dealing with. Here we have pipes, hold-up tanks, pumps, gas absorption and desorption apparatus, a heat exchanger, and a filter. The component of this system which has been of most interest to our group at Caltech is the absorption part, the artificial lung. Just as in the case of the natural lung, its function is to absorb oxygen and give off carbon dioxide. In the one shown here, blood flows over a screen, and the oxygen and the blood are in direct contact. A major problem in the use of such systems is the deterioration of the blood which occurs after a few hours of passing through the machine. This limits the surgeon's operating time and prohibits the use of the device during the post-operative recovery period. To reduce blood damage, plastic membranes have been introduced between the blood and the gas, and this appears to help matters.



External circulatory system of a type used in heart surgery (from Heart-Lung Bypass *by Galletti and Brecher, Grune and Stratton, New York, 1962).*

ARTIFICIAL DEVICE	CURRENT STATUS OF DEVELOPMENT	DEVELOPMENT GOAL
LUNG	USED FOR A PERIOD OF HOURS DURING HEART SURGERY	USE OVER A PERIOD OF DAYS DURING RECOVERY
HEART	USED FOR A PERIOD OF DAYS AFTER HEART SURGERY (WITH INDIFFERENT SUCCESS)	PERMANENT IMPLANTATION
KIDNEY	INTERMITTENT USE IN FIXED LOCATIONS OVER A PERIOD OF YEARS	CONTINUAL USE OF A PORTABLE DEVICE

The chart above summarizes the current development of these devices and the goals we have set for future developments. In the case of the heart and kidney, we hope to develop permanent, portable devices, implanted if possible. In the case of the lung, we have set a more modest goal, perhaps, because our current achievements are more modest.

An idea of what we are aiming for is shown, (right) in the artificial kidney of the future.

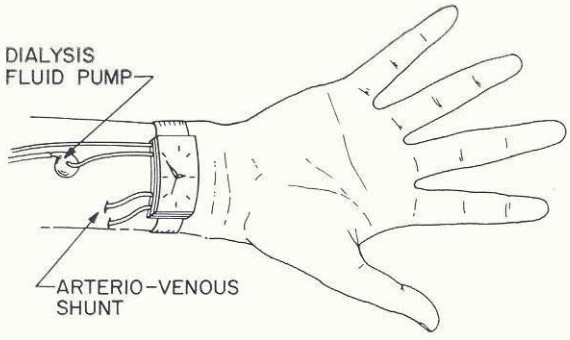
There are two major requirements associated with the design of these devices. First, in the case of the exchange devices (lungs and kidney), there is the need for an adequate rate of transfer of the molecular species of interest into or out of the blood. Second is the need to use materials of construction which do not damage the blood as the result of undesirable surface reactions. Some success has been achieved in both cases, but we still have a long way to go before we reach the transfer rates and non-toxic surfaces needed for prolonged used of compact devices.

The problems of exchange rates and non-toxicity are related because devices with large surface areas, hence greater exchange rates, are likely to produce more denaturation of the blood. Moreover, the denaturation products may collect at the surface and plug the membranes of the device. These two problems are interesting from an engineering point of

view. Engineers, who can do almost anything with air and water, turpentine and alcohol, are now trying to coax blood into acting like these other well-behaved fluids.

A cross section of a membrane oxygenator, an artificial lung, is shown at the right. Here we see the diffusion path which must be taken by a molecule of oxygen or carbon dioxide (or urea or creatinine). An oxygen molecule passes from the gas phase, wiggles its way through the membrane, and wanders around in the plasma until it chances upon a red blood cell. It enters the cell through a membrane before it finally reacts chemically with the hemoglobin in the cell. Carbon dioxide passes in the other direction. The blood is flowing on its side of the membrane, and the other fluid, oxygen flows on its own side. A similar picture could be drawn for the artificial kidney, except that the substances which must be removed from the blood include urea and creatinine, and saline solution instead of a gas flows along the opposite side of the membrane from the blood. Clearly a prime requirement is a membrane which will let the molecular species in question pass at a sufficiently rapid rate.

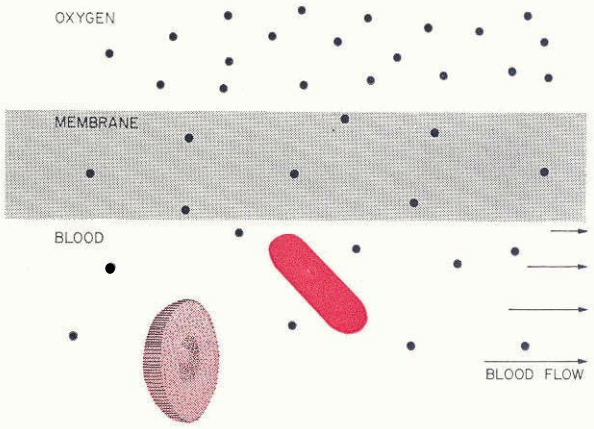
In some types of membranes there actually appear to be little holes or pores which are bigger than the molecules which want to pass through.



Artificial kidney of the future, as envisioned by Dr. L. W. Bluemle, Jr., of the University of Pennsylvania. The device would work continuously as part of the arteriovenous shunt using dialyzing fluid from a reservoir located on the patient's body.

The kinetic theory of matter tells us that molecules in fluids execute an endless dancing motion which allows them to penetrate these pores. More often, however, it appears that a rigid, sieve-like structure does not exist. Instead the diffusion of a molecule through the membrane can be likened to the passage of a marble through a ball of worms with the little wrigglers displaying the molecular motion of the polymeric segments composing the membrane. Here and there holes open up in the polymeric material only to close again as the chain-like molecules wriggle about.

For membrane lung design, silicone rubber has been found to be remarkably permeable to oxygen and carbon dioxide molecules. Using membranes



Schematic diagram of the oxygen-membrane-blood interfaces in the artificial lung. The film of slowly moving blood at the membrane surface inhibits oxygen absorption. Shown also are two red cells (viewed from different angles) with the one nearer the membrane more highly oxygenated.

one thousandth of an inch thick, Ed Spaeth, a Caltech graduate student in engineering, found that the major resistance to the passage of oxygen is a relatively thick, slowly moving film of blood which accumulates on the blood side of the membrane and inhibits exchange. When the blood film resistance controls, improving membrane performance adds little to the speed with which transfer occurs. It is a case of a very large and a very small resistance in series; reducing the magnitude of the smaller resistance results in little change in the current. Spaeth determined film thicknesses as a function of blood velocity and oxygen pressure. Films were thinnest at high velocities and at oxygen pressures which correspond to those found in the tissues of the body where the oxygen is released to the cells of the body. These experimental results and the theory which goes along with them represent a significant step forward toward the rational design of membrane oxygenators. Now for the first time we can predict film thicknesses, hence exchange rates, as a function of velocity for different geometric configurations of the oxygenator. This means that we can calculate surface area and total volume and determine optimal values for both.

The exchange situation for the artificial kidney is

in some ways more complicated than for the lung. There are more molecular species to deal with, and greater specificity in the performance of the membrane is necessary. Urea must be moved and, if possible, creatinine and uric acid as well. But the permeability must not be so great that larger protein molecules such as serum albumin can escape from the blood to the other side of the membrane. Such membranes are usually made of common cellophane. Their permeability can be controlled to a certain extent by dipping them in acids or other chemicals, and they do an adequate job of separation. To reduce kidneys to something approaching wristwatch size, still more effective membranes with unusual geometric configurations are needed. But development of improved membranes is a slow process, in part because the market for such materials is not sufficient to stimulate extensive research efforts. How to stimulate development? One suggestion has been to find a plastics manufacturer with a chronic kidney disease.

The improvement which results when patients suffering from chronic kidney disease are treated with the artificial kidney is not lost when urea is included in the dialysis bath, thereby blocking urea removal. This indicates that the undesirable effects are produced in the body not by the urea but by small quantities of other substances, as yet unidentified, which accumulate as a result of the reduction of kidney function until toxic concentrations are reached. The molecules of these agents must be small enough to be removed at the same time as urea by the dialysis membrane. Clearly this adds an element of uncertainty to membrane design. We can only *hope* that if known materials, such as urea, are passed by the membrane, the unidentified toxic agents will also get through!

Serious damage to the blood may occur as it passes through one of the devices. When blood is brought into contact with a foreign surface, coagulation takes place over a period of time which varies greatly with the nature of the surface. Even the least clot-promoting of polymers, silicone rubber, causes clots to form within 20 minutes in laboratory tests. The clotting time depends on a number of variables including the "wettability" of the surface and the surface electrical charge. Glass which is highly wettable induces clotting much more readily than a nonwettable material like paraffin. Clearly there must be more to the phenomenon than this, however, since the blood vessel walls themselves are highly wettable. The importance of electrical charges is indicated by experiments which have shown that clots form around a positive electrode placed in a blood vessel and are inhibited at the negative electrode. It is argued that the normal vascular wall is negatively charged and that damage to a vessel which produces clot formation also causes it to be positively charged.

Not only is clotting promoted as the blood passes through one of these devices, but the formed elements—red cells, white cells, and platelets—tend to break down. There are two schools of thought on the causes of hemolysis or red cell destruction. According to one, mechanical shear in the flow system rips the cells apart, although these may have previously been weakened by physico-chemical effects. According to the other, destruction results from the red cells hitting the walls of the flow system. The exact mechanism is not clear. Perhaps the delicate cell membrane adheres momentarily to the wall and is torn when the cell is pulled loose by the motion of the fluid.

Damage to the blood passing through an artificial external circulatory system during an operation has serious consequences. The clotting which is produced in the external circuit is countered internally by certain enzymes released by the body to dissolve the clots. The result is, on the one hand, a tendency toward premature clotting in the extracorporeal circuit and, on the other, the possibility of severe bleeding internally. Avoiding these dangers requires administration of correct dosages of the anticoagulant heparin and its neutralizing agent protamine at the proper times during the course of extracorporeal circulation procedure.

To further complicate matters, some of the constituents of the blood tend to deposit on foreign surfaces. For example, a fibrin coat forms on the inside walls of artificial hearts made of an impervious plastic in a matter of seconds after blood is introduced. The fibrin is produced by conversion of the protein fibrinogen, which is soluble in the plasma, into an insoluble form. The film builds up but is only loosely attached to non-porous plastic surfaces. Eventually it tears loose and disintegrates, appearing as an accumulation at both valves or embolized in the arterial system.

When blood flows through an artificial kidney, a layer of white cells deposits on the surface of the membrane. This effect is even more serious when the blood has been damaged. We have taken blood which had been circulated through a heart-lung machine during an operation—there is always a certain amount of blood needed to prime these devices and an equivalent amount remains at the end —and passed this "used" blood over a membrane to measure its diffusional resistance. Over a period of about two hours, the membrane resistance increased to about six times its original value, and

inspection of the membrane showed that a deposit of material from the blood had accumulated on the surface. No deposit or increase in resistance was observed in experiments with fresh blood.

How can we change the nature of the surface to prevent blood damage? One method used with artificial hearts takes advantage of the protein deposition phenomenon which I mentioned before. When an *impervious* plastic is utilized as an artificial substitute, the fibrin coat which deposits on its inner surface is anchored only at its ends, at the tissue connections. As a result the coat disintegrates rather easily and embolizes. Learning from this lesson, DeBakey's group places a nylon or dacron felt liner inside the plastic heart; when blood is introduced, a coating of fibrin develops on the felt which is so tightly bound that disintegration and embolization do not take place. The fibrin layer protects the blood from further contact with the foreign surface. When such liners are used, the level of plasma hemoglobin falls to preoperative levels indicating that red cell destruction is at a minimum. However, the possibility of applying this "grow your own skin" technique does not seem too promising for the large surface areas of extracorporeal circulatory devices.

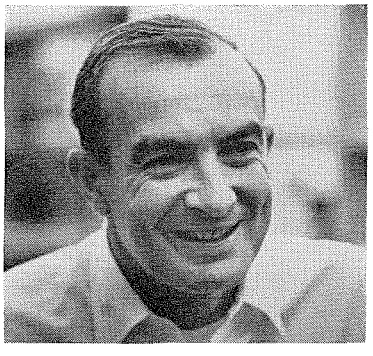
Another method which has been developed for inhibiting clotting is the alteration of the chemical nature of the surface over which the blood flows. One clever technique involves the bonding of heparin to the surfaces of polymeric materials. (Heparin is found in blood vessel walls as well as in the liver and lung tissue.) This is done by first incorporating in the surface layer a quaternary ammonium salt which has a special ability to bind heparin. The method is new and is currently being evaluated by implanting heparinized plastic rings in the veins of dogs. Polypropylene rings showed no evidence of clotting after a two-week period, but when polystyrene rings were used, about half had clots after the implantation period. Cellophane can also be treated with heparin, and membranes prepared in this manner retain their ability to dialyze.

Why surface-bound heparin inhibits coagulation is not known. Tests have shown no evidence of heparin *in* the blood which clots normally when coagulants are added so that it appears to be a true surface effect. While these developments sound promising, a serious problem remains: The hemolytic or red-cell-destroying character of almost all polymer surfaces increases several times when treated with heparin. Clearly the search must continue for a material with the compatibility of the internal surface of the healthy circulatory system.

The use of artificial devices, perfected to the point where they can sustain life over long periods of time, will increase the dilemma faced by modern medical practitioners who can maintain life, of a sort, long after a creature has ceased to function effectively as a human being. One can conceive of situations in which, by accident or as a result of disease, one organ ceases to function while the others continue to perform in a satisfactory manner. In such a case, the substitution of an artificial organ would be an obvious solution. On the other hand, old age, while it may result in the complete breakdown of only one organ, may be accompanied by the general deterioration of others as well as the nervous system. Should the substitution of the new organ for the old be made?

The question might become academic (in the worst sense of the word) if bioengineers of the future are able to grow entire new creatures from single cells of that creature. Then instead of replacing worn-out parts, there will exist the possibility of trading in an old model for a new one *of the same type.*

While I will not speculate any further on these questions, I will not disclaim interest or responsibility on the grounds that I am merely a technician and that the decisions must be made by politicians and theologians. The responsibility of scientists to participate in decisions concerning the applications of their brain children is important.



"Plastic Hearts, Membrane Lungs, and Artificial Kidneys—The Engineering of Vital Organs" has been adapted from a lecture given by Sheldon K. Friedlander at Caltech's 30th Annual Alumni Seminar on April 22. Dr. Friedlander is professor of chemical and environmental health engineering at the Institute. The major areas of his research are concerned with the application of engineering methods to problems of health and medicine. Research studies done recently under his supervision include work on the characteristics of high-speed beams of small particles, the mathematical theory of the particle size distribution of coagulating dispersions, and the diffusion of gases in flowing blood. Dr. Friedlander became involved with current developments in artificial organs, while working on the flowing blood project.