
7.5 Artificial Red Blood Cell Substitutes

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INTRODUCTION

The potential presence of HIV in donor blood in the 1980s was the main stimulus leading to serious development of the idea of modified hemoglobin started many years ago (Chang, 1957, 1964, 1965; Bunn and Jandl, 1968). Much progress has been made in the past 10 years leading to the final phase of phase III clinical trials before routine clinical application. The present modified hemoglobin can replace the plasma component and red blood cell component of blood. However, it cannot replace the platelets or the leukocytes of blood. During this period, much experience has been gained and much has been learned (Chang, 1997a). This chapter is a brief overview of this very large area. The readers are referred to much detailed description in the references (Chang, 1997a, 2000, 2002), which is updated on the Web site (www.artcell.mcgill.ca).

HEMOGLOBIN

Hemoglobin is the protein in red blood cells that is responsible for the transport of oxygen from the lung to the other tissues. When hemoglobin is extracted from red blood cells, it can be ultrafiltered and sterilized to remove and inactivate bacteria, viruses and other microorganisms. Thus unlike red blood cells, potential problems related to HIV, hepatitis viruses, parasites, and others could be eliminated. However, hemoglobin extracted from red blood cells cannot be used as a blood substitute for the following reasons. Each hemoglobin molecule is a tetramer consisting of four subunits—two alpha subunits and two beta subunits (Perutz, 1980) (Fig. 1). There is a requirement for 2,3-diphosphoglycerate (2,3-DPG) to be present in the 2,3-DPG pocket of the hemoglobin molecule. This is to decrease the affinity of hemoglobin for oxygen, thus allowing it to release oxygen properly. When infused into the body, there is little or no 2,3-DPG in the plasma to bind to the 2,3-DPG pocket. This results in hemoglobin with high affinity for oxygen, preventing oxygen from being easily released as required to the tissue. What is even more of a problem is that when free in the circulating blood, each hemoglobin molecule breaks down into potentially toxic half-molecules, dimers. The dimers are highly toxic especially their renal toxicity (Savitsky et al., 1978), There are also other problems related to hemoglobin in free solution. The challenge is therefore to modify the basic biomaterial, hemoglobin, before it can be used as a blood substitute.

MODIFIED HEMOGLOBIN

Polyhemoglobin

The first modified hemoglobin was formed by removing the biological cell membranes of red blood cells and replacing them with artificial membranes (Fig. 1) (Chang, 1957, 1964, 1965). These early artificial red blood cells can readily bind and release oxygen since 2,3-DPG is retained inside the artificial cells (Chang, 1957). However, although they are about the same size as red blood cells, they are not sufficiently flexible to allow them to survive for a long time after infusion. A number of approaches were used to change the surface properties of these artificial red blood cells (Chang, 1964, 1965, 1972). This includes surface modification to result in changes in surface charge, surface composition and membrane composition. Since hemoglobin has many surface and internal amino groups, Chang (1964, 1965, 1972) studied the use of a bifunctional agent, sebacyl chloride, to cross-link hemoglobin molecules into a cross-linked hemoglobin artificial red blood cell membrane. By decreasing the diameter, all the hemoglobin in the artificial red blood cells could be cross-linked into polyhemoglobin (Fig. 2). The reaction is as follows:

\[ \text{Cl–CO–(CH}_2\text{)}_x\text{–CO–Cl} + \text{HB–NH}_2 \]

Sebacyl chloride  Hemoglobin

= \text{HB–NH–CO–(CH}_2\text{)}_x\text{–CO–NH–HB}  

Cross-linked hemoglobin

In 1971, Chang reported the use of another bifunctional agent, glutaraldehyde, to cross-link hemoglobin and a red blood cell
enzymes, catalase, into soluble polyhemoglobin (Fig. 2). The reaction is as follows:

\[
H - CO - (CH_2)_2 - CO - H + HB - NH_2
\]

Glutaraldehyde          Hemoglobin

\[
= HB - NH - CO - (CH_2)_2 - CO - NH - HB
\]

Cross-linked hemoglobin

Cross-linking hemoglobin into soluble hemoglobin prevents the breakdown of hemoglobin into dimers. Furthermore, when infusing modified hemoglobin, their colloid osmotic pressure should normally be about the same as that of plasma proteins. This means that only about 7 g/dl of hemoglobin can be infused. Now, colloid osmotic pressure depends on the number of solute particles more than on the total amount of protein in solution. Polyhemoglobin is formed from the cross-linking of an average of four or five hemoglobin molecules together into a soluble macromolecular complex. This way, 15 g/dl of polyhemoglobin would have about the same colloid osmotic pressure as 7 g/dl of hemoglobin (Chang, 1997a). This means that a much larger amount of hemoglobin can be used when in the form of polyhemoglobin. However, there is no 2,3-DPG in the polyhemoglobin to allow them to have lower affinity for oxygen so that they can release oxygen to the tissue as required. Benesch et al. in 1973 made the important finding that the addition of a 2,3-DPG analog, pyridoxal phosphate, to hemoglobin can also decrease oxygen affinity (Fig. 2). This is therefore added to cross-linked hemoglobin to prevent dimer formation and improve oxygen affinity.

The 1971 glutaraldehyde approach of Chang has been combined with Benesch's use of pyridoxal phosphate and developed into pyridoxalated human polyhemoglobin blood substitutes by Dudziak and Bonhard in 1976; Moss' group (Sehgal et al.) in 1980; DeVenuto and Zegna in 1982; and Chang's group (Keipert et al.) in 1982. The Northfield group of Gould et al. (1998) has developed this very extensively to its present refined state. At present, Gould's group has completed phase II clinical trial and showed in control studies that this is effective in replacing blood loss in surgical patients. They are now in phase III clinical trial in trauma surgery using replacement of up to 10,000 ml which is equal to twice the total blood volume of a patient (Gould et al., 1998). This approach has also been developed extensively by the Biopure group (Pearce and Gawryl, 1998) using bovine polyhemoglobin to form bovine polyhemoglobin. Since hemoglobin from cows does not need 2,3-DPG to decrease the affinity for oxygen, pyridoxal phosphate is not required. They have completed their phase II clinical trial in patients and have started phase III clinical trial using as much as 11,000 ml in individual patients'. Biopure's veterinary product has been approved by the FDA for routine use in canine veterinary medicine. Clinical trials on the Biopure Polyhemoglobin (Sprung et al., 2002; LaMuraglia et al., 2000) have led to its being approved for routine clinical uses in South Africa (Lok, 2001) and awaiting approval in the United States. Hsia (1991) originated a dialdehyde prepared from open ring sugars to form polyhemoglobin. This cross-linker also modified the 2,3-DPG pocket so that the resulting polyhemoglobin does not require 2,3-DPG or pyridoxal phosphate. This has been developed and extended by Hemosol (Adamson and Moore, 1998), which has completed phase II clinical trial and is proceeding to phase III clinical trial.

**Other Types of Soluble Modified Hemoglobin**

Bunn and Jandl (1968) cross-linked hemoglobin intramolecularly and found that this prevents the loss of hemoglobin through the kidney and serves to decrease renal toxicity. Waldet et al. in 1979 reported the use of a 2,3-DPG pocket modifier, bis (3,5-dibromosalicyl) fumarate (DBBF) to intramolecularly cross-link the two α subunits of the hemoglobin molecule forming tetrameric hemoglobin. This prevents dimer formation and improves \( P_{50} \) in the case with which oxyhemoglobin releases its oxygen and is measured by the oxygen tension at which 50% of the oxygen is released from oxyhemoglobin. Unlike polyhemoglobin, cross-linked tetrameric hemoglobin is a single hemoglobin molecule. Although its molecular weight is comparable to that of albumin, hemoglobin has much less surface negative charge. As a result, it can cross the intercellular junction of the endothelial cells lining the vasculature much more readily (Fig. 5). This may have resulted in the removal of nitric oxide. Nitric oxide decreases the contraction of smooth muscles including those in vasculature. This may explain the increase in esophageal and intestinal contractions and increase in blood pressure when using these types of cross-linked tetrameric hemoglobin. Baxter has extensively developed this (Nelson, 1998), but the results of their clinical trials have led them to discontinue this approach and to look at another approach.

Another very exciting area is the use of recombinant technology to produce recombinant human hemoglobin from *Escherichia coli* (Hoffman et al., 1990). This results in the fusing of the alpha subunits of the hemoglobin molecule and preventing the breakdown of hemoglobin into dimers. Furthermore, this also resulted in the modification of the 2,3-DPG...

Different types of modified hemoglobin contain a varying amount of tetrameric hemoglobin that can also act similarly. Removal of these smaller tetrameric hemoglobin from polyhemoglobin, conjugated hemoglobin and microencapsulated hemoglobin would prevent this. Reprinted with permission from Chang, T. M. S. (1997). Artificial Cells, Blood Substitutes and Immunobilization Biotechnology 25:1–24. Courtesy of Marcel Dekker, Inc.

FIG. 3. Different types of modified hemoglobin (Hb). Tetrameric Hb being smaller can move across the intercellular junction of the endothelial cells. This Hb binds nitric oxide (NO) in the interstitial space and lowers the NO concentration. This results in vasocostriction. Other types of modified hemoglobin contain a varying amount of tetrameric hemoglobin that can also act similarly. Removal of these smaller tetrameric hemoglobin from polyhemoglobin, conjugated hemoglobin and microencapsulated hemoglobin would prevent this. Reprinted with permission from Chang, T. M. S. (1997). Artificial Cells, Blood Substitutes and Immunobilization Biotechnology 25:1–24. Courtesy of Marcel Dekker, Inc.

Pocket in such a way that there is no requirement for 2,3-DPG or pyridoxal phosphate. This has been developed by Somatogen and used in a phase II clinical trial (Freytag and Templeton, 1997). Being a single tetrameric hemoglobin, it can also cause the same effect on smooth muscle as described above for cross-linked tetrameric hemoglobin. They have now prepared a new generation of recombinant human hemoglobin in which they have blocked the binding site for nitric oxide (Doherty et al., 1998). The resulting recombinant human hemoglobin no longer causes vasocostriction. This is being developed by Baxter toward a clinical trial.

Chang (1964, 1965, 1972) has used interfacial polymerization to form a conjugated membrane consisting of polyamides and hemoglobin around hemoglobin. By decreasing the diameter of the conjugated membrane, all the hemoglobin can be cross-linked with polymer into conjugated hemoglobin. Wong (1998) cross-linked hemoglobin to dextran to form soluble conjugated hemoglobin. A PEG-conjugated bovine hemoglobin is now in phase II clinical trial (Short et al., 1996). A conjugated human hemoglobin (Iwashita et al., 1996) is also in phase II clinical trial.

**Molecular Weight Distribution**

Molecular weight (MW) distribution varies widely among the different types of cross-linked hemoglobin blood substitutes (Chang, 1997a). For intramolecularly cross-linked hemoglobin or recombinant hemoglobin, they are in the tetrameric form with a molecular weight of about 68,000. In polyhemoglobin the molecular weight distribution can vary widely. In polyhemoglobin, the molecular weights follow a distribution curve from tetrameric to much larger molecular weight. Some groups use a larger mean molecular weight. Other groups prefer using a smaller mean molecular weight. Those with lower mean molecular weight also have more tetrameric hemoglobin. Those with higher mean molecular weight have less tetrameric hemoglobin because of the higher degree of polymerization. The pyridoxalated polyhemoglobin prepared from our laboratory procedure can be used as an example. The molecular weight distribution can be varied at will by changing the reaction time, ratio of gluteraldehyde to hemoglobin, and other reaction parameters. To measure the MW distribution, pyridoxalated polyhemoglobin (PP-PolyHb) was run on Sephadex G-200 (1.6 × 70 cm column) in 0.1 M Tris-HCl (pH 7.5) at 12 ml/hr. The fractions of polymerized hemoglobin were in the molecular weight ranges of 750,000 (10%); 470,000 (23%); 260,000 (39%); 130,000 (21%); and 66,000 (7%). Thus, 60% falls in the 130,000–350,000 range and 33% ranges in molecular weight from 350,000 to 750,000. Only 7% was in the tetrameric form. Gould’s group (1998) has emphasized the need to remove as much tetrameric hemoglobin as possible. After their preparation of polyhemoglobin, they carried out another step to remove much of the tetrameric hemoglobin resulting in a preparation with less than 1% hemoglobin in the 68,000 MW range. Biopure has also removed much of the tetrameric hemoglobin resulting in preparation with less than 5% 68,000 MW hemoglobin (Pearce and Gawryl, 1998). These two preparations do not cause vasocostriction or smooth muscle contraction because insignificant amounts of tetrameric hemoglobin crossing the endothelial cell junctions (Fig. 3).

**In Vitro Biocompatibility Screening Test Using Human Plasma/Blood**

Detailed in vitro and in vivo tests are required by the FDA before approval of using the blood substitutes for clinical trials (Fratantoni, 1991). However, even when the blood substitute is shown safe in animals, the response in animals is not always the same as for humans. This is especially true in tests for hypersensitivity, complement activation, and immunology. How do we bridge the gap between animal safety studies and use in humans? Complement activation is important in many adverse reactions of humans to modified hemoglobin (Chang and Lister, 1990, 1993a, b, 1994). Modified hemoglobin may be contaminated with trace amounts of blood-group antigen that can form antigen–antibody complexes. Other materials can potentially cause complement activation. These include endotoxin, microorganisms, insoluble immune complexes, chemicals, polymers, organic solvents, and others.

We have devised an in vitro test tube screening tests using human plasma or blood (Chang and Lister, 1990, 1993a, b, 1994). The use of human plasma or blood gives the closest response to human testing next to actual injection. If we want to be more specific, we can use the plasma of the same patient who is to receive the blood substitute. Many components of human blood or plasma can be used for this in vitro screening test. If one were to select only one test, perhaps the most useful one would be the effect of modified hemoglobin on complement activation (C3a) when added to human plasma or blood. This simple test consists of adding 0.1 ml of modified
hemoglobin to a test tube containing 0.4 ml of human plasma or blood. Then, the plasma is analyzed for complement activation after incubation for 1 hour. Blood preparation is described in Table 1.

Blood is obtained by clean venous puncture from human volunteers into 50-ml polypropylene (Sastedt) heparinized tubes (10 IU heparin/ml of blood). Immediately separate plasma by centrifugation at 5300 g at 2°C for 20 min and freeze the plasma in separate portions at −70°C. Do not use serum because coagulation initiates complement activation. EDTA should not be used as an anticoagulant, because it interferes with complement activation.

The exact procedure and precise timing described in Table 1 are important in obtaining reproducible results. The baseline control level of C3a complement activation will vary with the source and procedure for obtaining the plasma. Therefore, a control baseline level must be used for each analysis. Furthermore, all control and test studies should be carried out in triplicate. Much practice is needed to establish this procedure when used for the first time. Reproducibility must be established before this test can be used.

Instead of using plasma and the need to withdraw blood from finger pricks (Chang and Lister, 1993a). Sterile methods are used to prick a finger. Blood is collected in heparinized microhematocrit tubes. The tubes are kept at 4°C and used immediately. Each blood sample used in testing contains 80 µl of whole blood and 20 µl of saline. Each test solution is added to a blood sample. Test solutions include saline (negative control); Zymosan (positive control); or hemoglobin. This is incubated at 37°C for 60 rpm. After 1 hour of incubation, EDTA solution is added to the sample to stop the reaction. The analysis for C3a is then carried out as described. The test kit is based on the ELISA C3a enzyme immunoassay (Quidel Co., San Diego).

In research, development, or industrial production of blood substitute, different chemicals, reagents, and organic solvents are used. This includes cross-linkers, lipids, solvents, chemicals, polymers, and other materials. Some of these can potentially result in complement activation and other reactions in humans. Other potential sources of problems include trace contaminants from ultrafilters, dialyzers, and chromatography. The test described in Table 1 is a simple in vitro test based on using human plasma or blood. For example, this screening test can detect several problems related to potential hypersensitivity reactions, and anaphylactic reactions, effects due to antibody–antigen complexes, and others. These potential problems may be related to contamination with trace blood group antigens, polymeric extracts, organic solvents, emulsifiers, and others. This is useful for preclinical trial studies and for screening before clinical use. This is also useful for screening batches of modified hemoglobin blood substitutes for industrial production to rule out potential problems. It is also useful in research and development. What is very exciting is that this approach may be the basis of a large-scale in vitro “clinical trial” in a large number of patients without infusing the product. By doing this, we can analyze the percentage of patients who may have adverse reactions without having to introduce the product into patients. Of course, ultimately, human clinical trials are required.

**Second-Generation Modified Hemoglobin Blood Substitutes**

The present, first-generation blood substitutes described above are effective for short-term uses especially in elective surgery (Winslow, 1996; Chang, 1997a). On the other hand, these first-generation blood substitutes can stay in the body’s circulation only for about 12–24 hours (a typical red blood cell lasts about 100 days). Thus, their present role is restricted to short-term applications. For example, substitutes are being tested in humans for replacing blood lost during some cardiac, cancer, orthopedic, and trauma surgeries. Furthermore, new generations of blood substitutes may be needed for other conditions such as sustained hemorrhagic shock, stroke, or other conditions with sustained ischemia (low oxygen). When oxygen from blood substitute is reperfused to ischemic organs or tissues, oxygen radicals will be produced (Fig. 4). The present generation of blood substitutes do not have the enzymes needed to protect the body against oxidants such as oxygen radicals. Unchecked, oxygen radicals may cause reperfusion injuries and other problems (Alayash et al., 1998). Furthermore, peroxide formed can break down hemoglobin resulting in further increase in oxygen radicals (Fenton reaction). Researchers are studying ways to solve this problem, including cross-linking the required enzymes to the hemoglobin or further modifying the molecular structure of the hemoglobin. For example, we have reported the cross-linking of superoxide dismutase (SOD) and catalase to hemoglobin to result in polyhemoglobin-catalase-SOD (Fig. 4) (D’Agnillo and Chang, 1998a,b; Chang et al., 1998). In a rat intestinal ischemia-reperfusion model, we showed that polyhemoglobin–catalase-SOD can markedly decrease the level

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Screening Test Based on Complement Activation (Chang and Lister, 1990, 1993a, b, 1994)</th>
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<tbody>
<tr>
<td>1</td>
<td>Immediately before use, the plasma sample is thawed.</td>
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<tr>
<td>2</td>
<td>400 µl of the plasma is pipetted into 4-ml sterile polypropylene tubes.</td>
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<tr>
<td>3</td>
<td>100 µl of pyrogen-free saline (or Ringer’s lactate) for injection is added to the 400 µl of heparinized plasma as control; 100 µl of hemoglobin or modified hemoglobin is added to each of the other tubes containing 400 µl of human plasma.</td>
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<tr>
<td>4</td>
<td>The reaction mixtures are incubated at 37°C at 60 RPM for 1 hour in a Lab-Line Orbit Environ Shaker (Fisher Scientific, Montreal, Canada).</td>
</tr>
<tr>
<td>5</td>
<td>After 1 hour the reaction is quenched by adding 0.4 ml of this solution into a 2 ml EDTA sterile tube containing 1.6 ml of sterile saline.</td>
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<tr>
<td>6</td>
<td>The samples are immediately stored at −70°C until analysis.</td>
</tr>
<tr>
<td>7</td>
<td>The analytical kit for human complement C3a is purchased from Amersham Canada. The method of analysis is the same as the instructions in the kit with two minor modifications. Centrifugation is carried out at 10,000 g for 20 min. After the final step of inversion, the inside wall of the tubes is carefully blotted with Q-Tips.</td>
</tr>
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</table>
of oxygen radicals when using polyhemoglobin with the cross-linked enzymes (Razack et al., 1997). Unlike polyhemoglobin, cross-linked polyhemoglobin-superoxide dismutase-catalase supplies oxygen without causing blood-brain barrier disruption or brain edema in a rat model of transient global brain ischemia–reperfusion (Pownada and Chang, 2002).

Third-Generation Blood Substitutes

Second-generation substitutes, like the first-generation blood substitutes, only circulate with a half-time of 12–24 hours. They are therefore more suitable for shorter term applications. Furthermore, the hemoglobin molecules will not be protected by a red blood cell membrane and highly purified hemoglobin is needed. Thus, researchers are working on more complicated, third-generation blood substitutes that will encapsulate hemoglobin and the required enzymes inside artificial red blood cells. Encapsulated hemoglobin is the first modified hemoglobin studied (Fig. 1) (Chang, 1957, 1964, 1972), but being more complicated, it has only been seriously developed more recently. One method is to encapsulate hemoglobin inside lipid vesicles about 0.2 µm in diameter (Djordjevich and Miller, 1980; Rudolph et al., 1997; Tsuchida, 1995). This technique also increases the circulation time. A more recent approach is to use nanotechnology methods to encapsulate hemoglobin and enzymes inside biodegradable poly(lactic acid) membrane nanocapsules some 0.15 µm in diameter (Yu and Chang, 1986; Chang and Yu, 1997, 1998) (Fig. 5). Nano-dimension artificial red blood cells with ultrathin membranes of poly(ethylene glycol)–poly(lactide) copolymer stay in the circulation twice as long as polyhemoglobin (Chang and Yu, 2001).

Earlier Perfluorocarbons: Fluosol-DA

Fluosol-DA is a 20% (w/v) mixture of seven parts of perfluorodecalin and three parts perfluorotripropylamine, with 2.7% Pluronic F-68 as an emulsifier and 0.4% egg yolk phospholipids to form a membrane coating on the emulsion. The average particle size of the emulsion is 0.118 µm. Because of the viscosity of the fluorocarbon emulsion at high concentrations, the maximum amount used is only 20%. Patients have to breathe 70% to 90% oxygen for this amount of fluorocarbomer to carry enough oxygen. The amount of oxygen dissolved in fluorocarbon determines the amount of available oxygen. When oxygen is increased to 70–90% from the atmospheric oxygen of 20%, more oxygen is dissolved in the fluorocarbon. CO₂ also dissolves in the fluorocarbon, which carries it to the lung for elimination. Mitsuno and Ohyanagi (1985) reviewed the Japanese experience with 401 patients who received Fluosol-DA (20%).
Complement activation was the major clinical problem. Adverse effects were observed in some patients due to complement activation caused by the Pluronic surfactant used in FlussoL. The FDA approved the clinical use of FlussoL-DA only for coronary artery balloon angioplasties in 1989.

**Modern Perfluorochemicals**

Modern perfluorochemicals have been discussed in detail (Riess, 1998; Keipert, 1998). Two new types of preparations have been developed. One type is based on perfluorocetyl bromide \((\text{CF}_8\text{F}_{17}\text{Br})\) and perfluorodichloroctane \((\text{CF}_8\text{F}_{16}\text{Cl}_2)\). Both types allow the use of higher concentrations of PFC. Oxygen from Alliance Pharmaceutical Corp., San Diego, is prepared from perfluorocetyl bromide \((\text{CF}_8\text{F}_{17}\text{Br})\) with egg yolk lecithin as the surfactant. The use of egg yolk lecithin instead of Pluronic surfactant has solved the problem of complement activation. Another approach, Oxyfluor from HemoGen, St. Louis, is based on the use of perfluorodichloroctane \((\text{CF}_8\text{F}_{16}\text{Cl}_2)\) with triglyceride and egg yolk lecithin.

Safety clinical trials using Oxygent show that doses up to 1.8 g PFC/kg could be given without side effects (Keipert, 1998). Further increase in dosages may result in transient mild febrile response \((38–39\, ^\circ\, \text{C})\), a transient decrease in platelets. Oxygen is being used in phase II clinical trials in surgical patients. The use of 0.9 g/kg of Oxygent can avoid the need for 2 units of blood. This is also being combined with autologous blood predilution in which about 1000 ml of each patient’s blood is removed and stored before surgery. During surgery, Oxygent is given as needed. After surgery, the patient’s blood is reinfused. There are several other potential applications for perfluorochemicals. One of the most important potential use is in patients who because of religious beliefs cannot use red blood cells or hemoglobin from animal sources.

**GENERAL DISCUSSION**

The basic ideas of cross-linked hemoglobin and encapsulated hemoglobin date back to before the 1960s. Concentrated efforts to develop blood substitutes for human use only seriously started after 1986 because of public concerns regarding HIV in donor blood. Unfortunately, a product must undergo years of research and development followed by clinical trials before it is ready for use in patients. It will take at least another one to two years for the first generation blood substitutes to be available for routine use. Had there been a serious development effort in the 1960s, blood substitutes would have already been available in 1986. As it is, the public has continued to be exposed to the potential, though extremely rare, hazard of HIV in donor blood. It is hoped that investigators will have the chance to develop new generations of blood substitutes discussed here long before another urgent need arrives. The principle of artificial cells has also been developed for other areas of medical applications including enzyme therapy, cell therapy, and other applications (Chang, 1997b; Chang and Prakash, 1998, 2001) (www.artcell.mcgill.ca).

**Bibliography**


7.6 Extracorporeal Artificial Organs
Paul S. Malchesky

Historically, the term “extracorporeal artificial organs” has been reserved for life-support techniques requiring the on-line processing of blood outside the patient’s body. The substitution, support, or replacement of organ functions is performed when the need is only temporary or intermittent support may be sufficient. The category of extracorporeal artificial organs does not include various other techniques that may justifiably be considered as such, such as infusion pumps or dermal patches for drug delivery, artificial hearts used extracorporeally, eyeglasses and contact lenses for vision, and orthotic devices and manipulators operated by neural signals to control motion.

This chapter focuses on artificial organ technologies that perform mass-transfer operations to support failing or impaired organ systems. The discussion begins with the oldest and most widely employed kidney substitute, hemodialysis, and outlines other renal assist systems such as hemofiltration for the treatment of chronic renal failure and fluid overload and peritoneal dialysis. The blood treatment process of hemoperfusion, and apheresis technologies, which include plasma exchange, plasma treatment, and cytapheresis—used to treat metabolic and immunologic diseases—are also discussed. In addition, blood-gas exchangers, as required for heart–lung bypass procedures, and bioartificial devices that employ living tissue in an extracorporeal circuit are addressed. Significant concerns and associated technological considerations regarding these technologies, including blood access, anticoagulation, the effects of the extracorporeal circulation, including blood cell and humoral changes, and the biomodulation effects of the procedure and materials of blood contact are also briefly discussed.

KIDNEY ASSIST

The kidney’s function is to maintain the chemical and water balance of the body by removing waste materials from the blood. The kidneys do this by sophisticated mechanisms of filtration and active and passive transport that take place within the nephron, the single major functioning unit in the kidney, of which there are about 1 million per kidney (Fig. 1). In the glomerulus, the blood entry portion of the nephron, a blood filtration process occurs in which solutes up to 60,000 Da are filtered. As this filtrate passes through the nephron’s tubule system, its composition is adjusted to the exact chemical requirements of the individual’s body to produce urine. In addition to these functions, the kidneys support various other physiological processes by performing secretory functions that aid red blood cell production, bone metabolism, and blood-pressure control. Renal failure occurs when the kidneys are damaged to the extent that they can no longer function to detoxify the body. The failure may be acute or chronic. In chronic renal failure or in the absence of a successful transplant, the patient must be maintained on dialysis. More than 300,000 people in the United States and more than one million worldwide are on dialysis.

Dialysis

Dialysis is the process of separating substances in solution by means of their unequal diffusion through a semipermeable membrane. The essentials for dialysis are (1) a solution containing the substance to be removed (blood); (2) a semipermeable membrane permeable to the substances to be removed and impermeable to substances to be retained (synthetic membrane