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HEMOPERFUSION, PLASMAPERFUSION AND OTHER CLINICAL USES OF GENERAL, BIOSPECIFIC, IMMUNO AND LEUCOCYTE ADSORBENTS

Edited by

Thomas Ming Swi Chang
Yoshihiro Endo
Volodymyr G Nikolaev
Tohru Tani
Yaoting Yu
Wen-Hui Zheng

World Scientific

HEMOPERFUSION, PLASMAPERFUSION AND OTHER CLINICAL USES OF GENERAL, BIOSPECIFIC IMMUNO AND LEUCOCYTE ADSORBENTS

Written by 30 worldwide leading scientists, experts and medical doctors, this comprehensive book provides a broad, multi-disciplinary overview on hemoperfusion. The research of the subject was started by TMS Chang - the pioneer and inventor of microcapsules who is well known as the "the Father of Artificial Cells and Bioencapsulation" The book presents the numerous recent developments in this field. A series of tailor-made, toxin removing and cell separating adsorbents or microcapsules with unique properties have been designed, prepared and produced for use in the treatment of disease such as autoimmune disease, drug over-dose, acute inflammation, etc,., in which ordinary medical treatments show little or no efficacy. Various modalities of hemoperfusion treatments and results are described to provide readers with up-to-date information on the highly interdisciplinary field of hemoperfusion.

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Chapter 1

First Design and Clinical Use in Patients of Surface Modified Sorbent Hemoperfusion Based on Artificial Cells for Poisoning, Kidney Failure, Liver Failure and Immunology

Thomas M.S. Chang*

1. Introduction

The introduction section starts with a brief historical overview and brief summary of the basic principles and the different areas of clinical use. The sections to follow will be detailed descriptions of the different areas. This chapter will be followed by 30 chapters that go over the present status in detail.

1.1. *A Brief Historical Overview*

Adverse effects of particle embolism and damage to blood cells had prevented the use of hemoperfusion using adsorbents like activated charcoal (Yatzidis, 1964; Dunea and Kolff, 1965) or resin (Winchester,

*Artificial Cells & Organs Research Centre, Department of Physiology, Medicine & Biomedical Engineering, Faculty of Medicine, McGill University, Montreal, QC, Canada, H3G1Y6.

1996). While carrying out research on artificial cells (Chang, 1964), my theoretical analysis showed artificial cells can be the basis of a very simple and inexpensive detoxifier that can be more effective than the standard hemodialyser (Chang, 1966). While continuing with basic research on the other aspects of artificial cells, I spent a major part of my early 15-year research career developing this idea followed by successful clinical trials and routine use in patients (Chang, 1966, 1969a, 1971d, 1973a, 1974c, 1974h, 1975i, 1976g, 1977b, 1980e).

In order to allow for more widespread development and use for patients, the following was carried out:

(1) The details of methods, procedures and results were immediately published in journals and in a monograph (Chang, 1972) that contained even more details. Thus when I was a Chinese Academy of Science visiting professor in 1978, I found that Professor W.H. Zheng in China was able to successfully prepare the device and use it in patients in China based only on my published details.

(2) Welcomed trainees and visiting scientists and clinicians from around the world.

(3) Freely gave advice to different groups and discussed the advantages and disadvantages of different approaches. The Medical Research Council of Canada supported research and clinical trials, which were carried out at McGill University. Thus instead of accepting the many foreign offers, I encouraged them to start a company in Montreal. Finally, Mr. Messeur sold his dialysis company in France and started a company in Montreal. I agreed to help if I did not have to sign an exclusive agreement. In return, I did not receive any consulting fee or stocks, and the company would give McGill University a research grant. The company also agreed to sell the device for not more than $35 each. Mr. Messeur was an excellent developer and collaborator, and together we scaled this up for production and clinical trials. My clinical trials at the McGill University teaching hospitals, especially the Royal Victoria Hospital, resulted in FDA approval for clinical use. It was so successful at $35 per device that a large US dialysis company bought it over despite my objection. Since I did not hold

any stock I had no vote on this. In any case, the US dialysis company increased the price for the device to about $300 almost overnight. At this price, it is no longer affordable or competitive with standard dialysis therapy. As a result, it is not being used much in Canada and the US. Fortunately, other countries have developed and produced this device with modifications and extensions. For instance, the Chinese products are effective and not costly, and as a result it is being used extensively there.

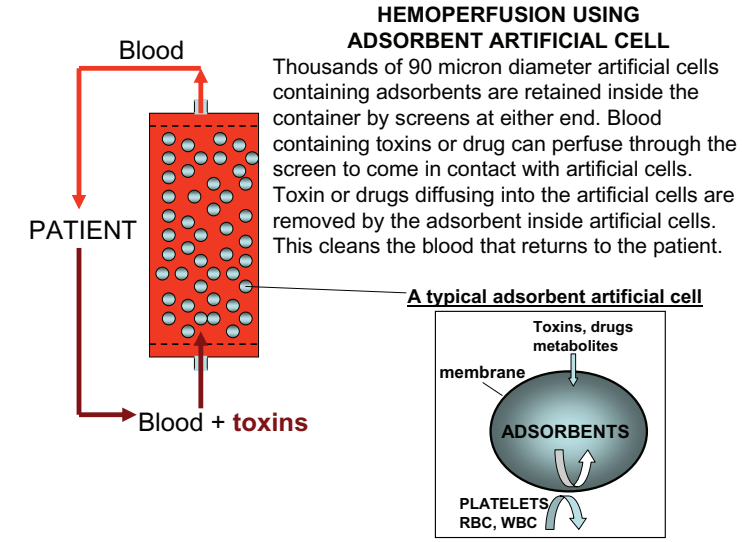
(4) Organized and coordinated an international symposium series on hemoperfusion rotating around the world starting at McGill (Chang) followed by Italy (Bonamini, Bologna U): Israel (Sideman, Technion); Turkey (Piskin, Ankara U); China (Huang, president of the Chinese Academy of Medical Sciences); Mexico (Trevino Becerra, Mexico U); USSR (Nikolaev, USSR Academy of Science); Germany (Klinkmann & Falkenhagen, Rostock); Japan (Odaka, Chiba U); Italy (Casciani & Splendiani, Rome U) and the US (Langer, MIT).

(5) When other centers and companies around the world became fully established to develop and extend this area, I discontinued the above series and moved my attention to other areas of artificial cells that need to be developed. This way, other centers can develop and extend this area without my interference in any way. This is important because the pioneer and originator can be very controlling and protective about his original approach.

As a result of 1 to 5 above, there is extensive development, extension and clinical use of this approach around the world as shown by the many chapters in this book.

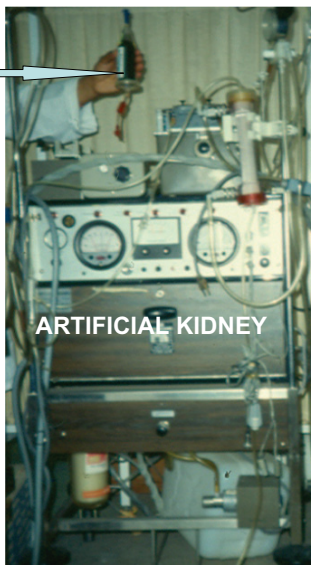
1.2. *Basic Principle of Surface Modifications Based on the Principle of Artificial Cells*

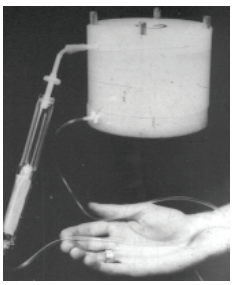
The principle will be described in detail later. Briefly it is based on thousands of 90 micron diameter adsorbent artificial cells in the form of microscopic surface modified adsorbent granules. These are retained inside a small container by screens at either end (Fig. 1.1).



Commercial device

Artificial cell Hemoperfusion device compared to an artificial kidney machine





Laboratory device prepared and used by Chang in first clinical trials (1970)

Fig. 1.1. *Upper*: Basic principle of adsorbent artificial cells in hemoperfusion. Lower left: Laboratory and commercial hemoperfusion devices. *Lower right*: Much smaller and simpler hemoperfusion device compared to an artificial kidney machine.

Blood from patients containing toxins or drugs perfuses through the screen of the container to come in contact with the artificial cells. Toxins or drugs diffusing into the artificial cells are removed by the adsorbent inside the artificial cells. This cleans the blood that returns to the patients. The membrane of the artificial cells prevents particles from the adsorbent from being released into the body and also prevents the adsorbent from damaging the blood cells (Chang, 1966) (Fig. 1.1). This solves the earlier problem of particle embolism and severe damage to blood cells when using unmodified adsorbents in hemoperfusion (Yatzidis, 1964; Dunea and Kolff, 1965).

1.3. *Clinical Trials*

There was extensive international and local support for this approach. Thus, Professor Kolff, the inventor of the artificial kidney, wrote the Canadian Medical Research Council that this approach should be extensively supported. Locally, McGill's human ethics committee having reviewed in detail all our preclinical safety and efficacy animal studies (Chang, 1969a, 1972a; Chang and Malave, 1970; Chang *et al.*, 1971a) approved the use of this device for clinical trials at McGill's teaching hospitals. At that time this was a very new idea, and although physicians were very supportive, they were concerned about liability and thus not ready to carry out this procedure in clinical trials in patients. Thus, the arrangement was for me to prepare the hemoperfusion devices in my laboratory then use them to personally carry out clinical trials on patients myself under the following protocol. The nephrologists at the dialysis units would refer patients to me. I would then make the final decision whether to carry out the procedure and to do the treatment on the patients myself. The Phase I safety study showed the safety of this in patients (Chang and Malave, 1970; Chang *et al.*, 1971a; Chang, 1972a), and as a result clinical trials on efficacy followed. The subsequent clinical trials meant being on call 24 hours a day over a number of years, and this was possible only because of the understanding of my wife, Lancy.

1.4. *Treatment of Patients with Severe Accidental or Suicidal Poisoning*

Clinical trial on its use in suicidal or accidental poisoning is more straightforward. The efficacy can be shown after one or two treatments, and the results can be assessed both quantitatively and clinically. Thus this was first successfully carried out in three patients (Chang *et al.*, 1973a, 1973b), then continued to a total of 11 adult patients (Chang 1975g, 1976c, 1980e) plus one pediatric patient (Chang *et al.*, 1980a) with conclusive clinical results. These will be discussed in more detail in a later section of this chapter. The results of these clinical trials have led to the routine use of this approach around the world for the treatment of drug poisoning (Better *et al.*, 1979; Biberstein *et al.*, 1983; Cohan *et al.*, 1982; Verpooten *et al.*, 1984; Gelfand *et al.*, 1977; Gibson *et al.*, 1978; Lorch and Garella, 1979; Winchester, 1996; Diaz-Buxo *et al.*, 1978; Sideman and Chang, 1980b; Piskin and Chang, 1982; Chang and Zheng, 1983; Chang and Ho, 1985; Chang and Nicolaev, 1987; Chang and Odaka, 1991; Klinmann *et al.*, 1990; Kawasaki, 2000; Lin *et al.*, 2002; Lopez-Lago *et al.,* 2002; Peng *et al.*, 2004; Chinese Symposium on Hemoperfusion, 2005, also chapters in this book).

The exact method of preparing artificial cells containing adsorbent has been published in reproducible detail for all to use (Chang, 1972a, 1976g). As a result, a number of countries, for instance, Canada, China, the US, the UK, Japan, Sweden, Italy, Spain and the former USSR were able to use this principle to produce their own variations of commercial hemoperfusion devices with the usual variations in efficacy and biocompatibility. While the inferior ones are no longer in use, those that are safe and effective are being used in routine clinical treatment of accidental and suicidal poisoning. For some unknown reasons, in some areas of the world, these devices are extremely expensive and as a result are too costly for widespread use. In other areas of the world, inexpensive but safe and efficient devices are being produced and used extensively, saving thousands of patients with potentially fatal accidental or suicidal poisoning.

1.5. *Hemoperfusion for the Removal of Unwanted or Toxic Substances from Blood in Other Conditions Including Terminal Renal Failure, Liver Failure and Immunology*

Hemoperfusion has been an established routine clinical method for the treatment of patients with severe suicidal and accidental poisoning for many years. Its ability to remove unwanted or toxic substances from the blood is also applicable in other clinical conditions. This includes its use in kidney failure, liver failure and use as an immunosorbent.

1.6. *Treatment of Patients with Terminal Kidney Failure*

Hemoperfusion in terminal kidney failure patients results in improvement in well-being and uremic symptoms (Chang *et al.*, 1971a, 1972g, 1974). It efficiently removes uremic wastes and toxins, especially the larger middle molecules (Chang, 1972e; Chang and Migchelsen, 1973; Chang and Lister, 1980, 1981). However, hemoperfusion does not remove electrolytes, water or urea. Thus, it has been used in series with hemodialysers with reported clinical improvements in "well-being," nerve conduction velocity, pruritis, pericarditis, peripheral neuropathy and, what is also important, reduction in treatment time (Chang *et al.*, 1975, 1982b; Martin *et al.*, 1979; Inou *et al.*, 1979; Odaka *et al.*, 1980; Agishi *et al.*, 1980; Stefoni *et al.*, 1980, also chapters in this book). It is also used for uremic patients with aluminium or iron overload based on the use of deferoxamine to bind these heavy metals and for hemoperfusion to remove the complex (Chang and Barre, 1983; Chang, 1986d; Chang *et al.*, 1984a, 1989a; Hakim *et al.*, 1985; Winchester, 1996).

In an attempt to eliminate the need or cost for the bulky and expensive hemodialysis machine, hemoperfusion has been used in series with a small ultrafiltrator with oral adsorbents to control potassium and phosphates (Chang *et al.*, 1975, 1977b, 1979a; Chang, 1976c). As will be described later, an oral urea removal system is being developed to complete the hemoperfusion-ultrafiltrator approach.

1.7. *Treatment of Patients with Hepatic Coma*

Its effectiveness in removing toxins from the circulating blood has also been shown in hepatic coma patients. Thus, the first use of this in a grade IV hepatic coma patient resulted in the recovery of consciousness within an hour (Chang, 1972b). As will be described later, this was followed by extensive clinical trials in hepatic coma patients around the world, showing that this is effective in removing hepatic toxins resulting in the recovery of consciousness in a significant number of patients (Chang, 1972b, 1975e, 1975j, 1976c, 1982a; Gazzard *et al.*, 1974; Blume *et al.*, 1976; Chang *et al.*, 1977a; Bartels *et al.*, 1977, 1981; Silk and Williams, 1978; Gelfand *et al.*, 1978; Gimson *et al.*, 1978; Odaka *et al.*, 1978; Amano *et al.*, 1978; Maeda *et al.*, 1980, Cordoatri *et al.*, 1982; William, 1983; O'Grady *et al.*, 1988, also chapters in this book). However, the liver is a complex organ with many other functions besides detoxification. Thus hemoperfusion has an important role in removing hepatic toxins to allow the use of dialysis or plasmapheresis to look after the other functions. Artificial cells containing hepatocytes and stem cells may also contribute to liver regeneration. These will be discussed later in this chapter and in even more detail in other chapters in this book.

1.8. *Immunoadsorbent and Specific Absorbents*

Albumin can bind tightly to the ultrathin collodion membrane of adsorbent artificial cells to increase the blood compatibility for hemoperfusion (Chang, 1969a). This albumin-coated collodion-activated charcoal (ACAC) was found to effectively remove antibodies to albumin in animal studies (Terman *et al.*, 1977). This has become a basis of one line of research in which other types of antigens or antibodies are applied to the collodion coating of the activated charcoal to form immunosorbents. Other immunosorbents based on this principle have also been developed for the treatment of human systemic lupus erythematosus, hyperacute renal xenograft rejection, and removal of antiHLA antibodies in transplant candidate treatment of familial hypercholesterolemia with monoclonal antibodies to low-density

lipoproteins (Terman, 1980; Terman *et al.*, 1979a, 1979b; Hakim *et al.*, 1990; Wingard *et al.*, 1991; Yang *et al.*, 2004, also chapters in this book). This surface modification was applied to synthetic immunosorbents resulting in blood compatible synthetic blood group immunosorbents (Chang, 1980d) and used clinically for removing blood group antibodies from plasma for bone marrow transplantation (Bensinger *et al.*, 1981). This has led to the use of different synthetic immunosorbents with modified blood compatible surfaces for the removal of antigen, antibody and even leucocytes. Synthetic adsorbents for the removal of endotoxin are also being used clinically. These will all be discussed in detail later in this chapter and in even more detail by other groups in a number of chapters in this book.

2. Detailed Analysis of the Principle of Artificial Cells in Surface Modification for Adsorbent Hemoperfusion

2.1. *Permeability and Transport Characteristics*

The artificial cell has an ultrathin membrane of less than 0.05 micron when compared to the 2.0 micron thickness of the dialysis membrane. Furthermore, the small size of artificial cells means that 30 mL of artificial cells can have a total surface membrane area of 2 m^2 compared to the 1 to 2 m^2 of a whole dialysis machine (Table 1.1, Fig. 1.2). This means that 30 mL of artificial cells can have a theoretical mass transfer that is 100 to 200 times that of a whole artificial kidney machine (Chang, 1966, 1972a) (Table 1.1).

Table 1.1. Analysis of Mass Transfer

	30 mL Artificial Cells	**1Artificial Kidney Machine**
Total surface area:	2 m^2	2 m^2
Membrane thickness:	0.02 μ ultrathin	2.00 μ
Mass transfer	100 ×	1

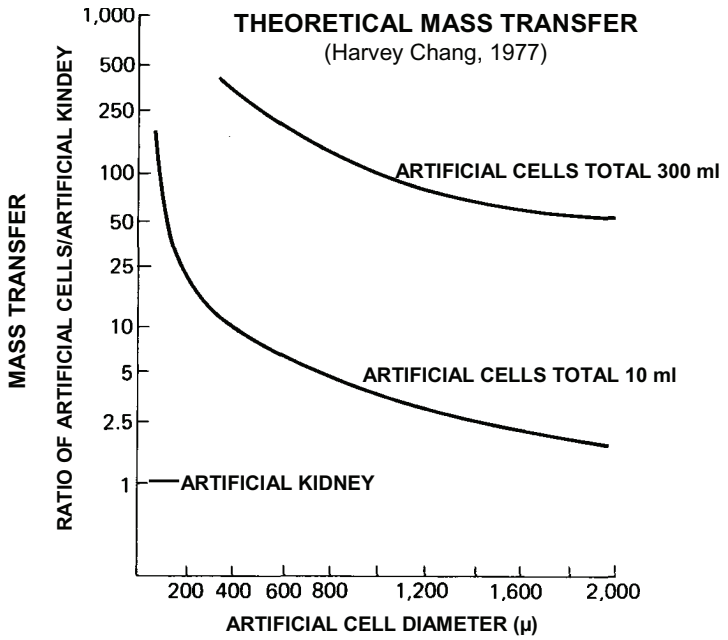


Fig. 1.2. Mass transfer of artificial kidney represented as 1. Ratio of mass transfer of 10 mL and 300 mL of artificial cells of different diameters. Hemoperfusion uses artificial cells of about 100 micron diameter (computer simulation by H. Chang).

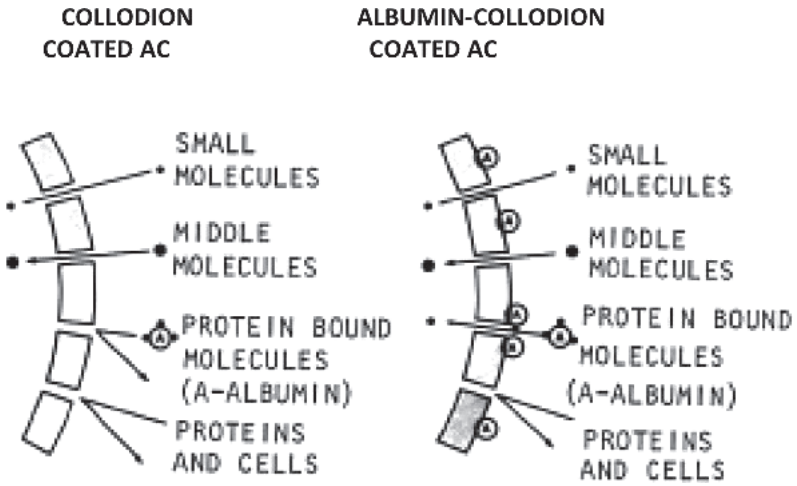


Fig. 1.3. *Left*: Ultrathin polymeric (collodion) membrane coating. *Right*: Ultrathin albumin-collodion membrane coating.

We also analyzed the effects of varying the diameter, and the total volume of artificial cells can be varied over a wide range. Figure 1.2 compares the mass transfer of artificial cells with that of a standard hemodialysis machine. Here, the mass transfer of a standard hemodialysis machine is taken as unity and compared to that of 10 ml and 300 ml of artificial cells of different mean diameters. Even with 10 ml of artificial cells, the mass transfer is many times that of the standard hemodialysis machine. With 300 ml of artificial cells, the mass transfer is even higher.

2.2. *Experimental Analysis*

Experimental study of typical artificial cells shows that the equivalent pore radius is 18 Å (Chang, 1965, 1972a). This means that the membrane would be permeable and also permeable to metabolites and peptides normally present in the body fluid. Detailed analysis of the rate of movement of different molecules has also been carried out (Chang and Poznansky, 1968a) (Table 1.2). These results show that metabolites normally present in the body can equilibrate very rapidly across the artificial cell membrane.

Table 1.2. Experimental Permeability Data for Artificial Cells

Solutes	Half-time for Equilibration (sec)	Permeability Constant (P) (cm/sec)	Solute Permeability Coefficient (W) (moles/dyne-sec.)
Urea	4.3	2.01×10^{-4}	8.23×10^{-15}
Creatinine	17.5	0.61×10^{-4}	2.52×10^{-15}
Uric acid	42.5	0.19×10^{-4}	0.77×10^{-15}
Creatine	16.6	0.75×10^{-4}	3.08×10^{-15}
Glucose	26.2	0.54×10^{-4}	2.17×10^{-15}
Sucrose	35.5	0.37×10^{-4}	1.62×10^{-15}
Actylsalicylate	39.0	0.32×10^{-4}	1.31×10^{-15}
Trtiated water	<1.0	N/A	N/A

This being the case, 30 ml of artificial cells retained in a shunt perfused by circulating blood will have the mass transfer of a whole artificial kidney machine (Chang, 1966) (Figs. 1.1, 1.2). However, in the case of the artificial kidney machine, once solutes cross the membrane they are "washed" away by 100–200 L of dialysis fluid. For artificial cells with a total internal volume of 30 ml, within a very short time, there will not be a concentration gradient for further solute diffusion. However, artificial cells are not meant to function as dialysers. They are made to function as microscopic bioreactors. This way, solute entering the artificial cells can be rapidly converted or removed, thus maintaining a concentration gradient. Thus our earlier study shows that artificial cells containing urease in a hemoperfusion chamber can rapidly lower blood urea, converting it to ammonium (Chang 1966). Adsorbents, like activated charcoal, placed inside artificial cells can also remove solutes that equilibrate rapidly inside (Chang, 1966). Why do we choose to use activated charcoal?

2.3. *Artificial Cells Containing Activated Charcoal in Hemoperfusion*

Activated charcoal has the ability to adsorb and remove a large spectrum of molecules. Since ancient times, the Chinese and the Greeks have used this for removing toxic substances. Activated charcoal has also been placed in a hemoperfusion device for direct perfusion by blood (Yatzidas, 1964). However, Dunea and Kolff (1965) showed in animal study that this resulted in (1) embolism due to the release of charcoal powder into the body and (2) this also damaged and removed blood cells, especially platelets.

By putting activated charcoal inside artificial cells, one can prevent particle release and also prevent the direct contact of blood cells (Chang, 1966) (Fig. 1.1). At the same time, unwanted molecules can move rapidly into the artificial cell and be removed by the activated charcoal.

In order to put this into practice, artificial cells were first prepared to contain activated charcoal powder (Chang, 1966). However, in a hemoperfusion device, the ultrathin membrane of the artificial cells cannot withstand the larger pressure gradient during perfusion.

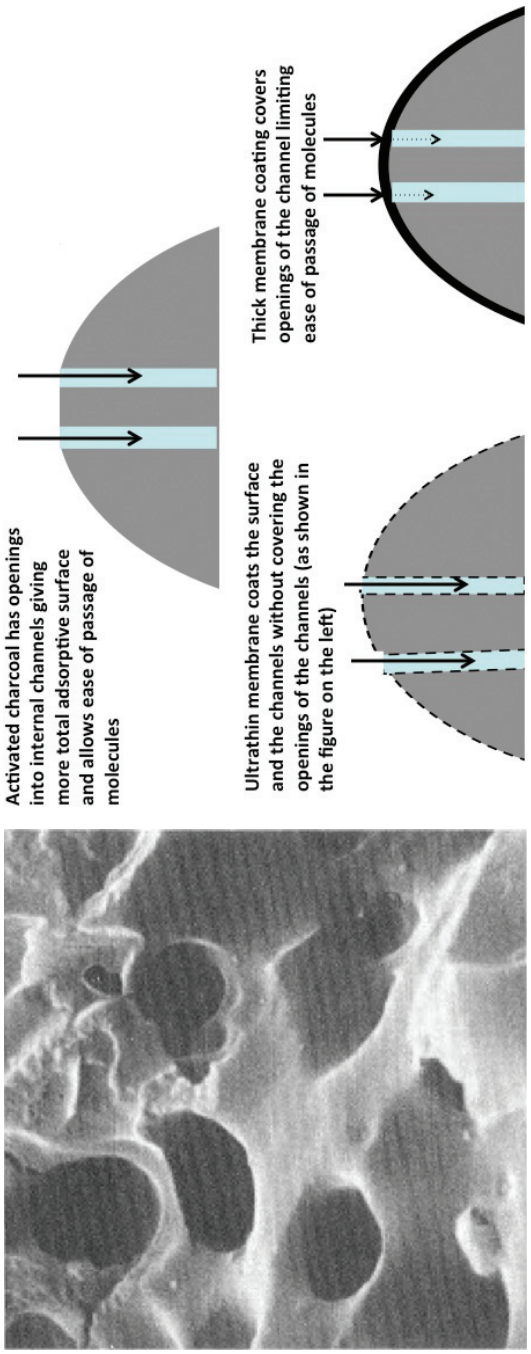


Fig. 1.4. A scanning electron-microscopic picture of ultrathin albumin-collodion membrane coated activated charcoal. The activated charcoal pores are not covered by the ultrathin membrane allowing for more efficient passage of molecules into the adsorbent.

Furthermore, the flexibility of the ultrathin membrane increases flow resistance and also packing and obstruction at the exit port of the hemoperfusion device. A more successful method is to coat the ultrathin membrane directly onto activated charcoal granules (Chang, 1969a). This way, there is no breakage of the ultrathin membrane, no increase in flow resistance and no obstruction to flow. Furthermore, an ultrathin membrane coating would not cover the pores of the activated charcoal surface and allows for better contact (Fig. 1.4). The ultrathin coating also results in the prevention of particle release. At the same time, this surface modification also results in a blood compatible surface with no damage to circulating blood cells. This forms the basis of all subsequent successful industrial approaches. However, those using a thick coating would result in decrease in permeability and mass transfer.

2.4. *Device Configuration*

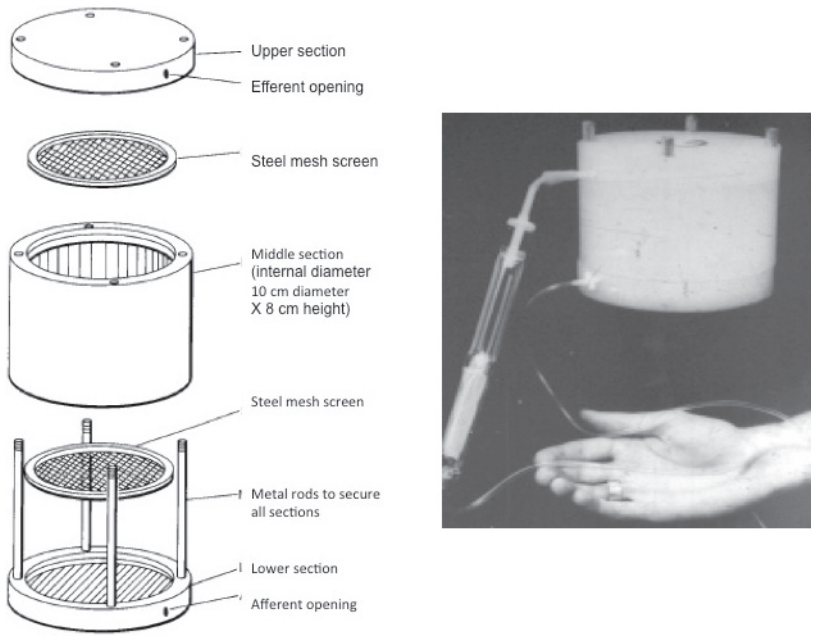


Fig. 1.5. Laboratory hemoperfusion device configuration. Screen on both sides retained the adsorbent artificial cells inside the column.

2.5. *Effects on Embolism*

In vitro studies show that there is no particle release since there is no significant difference in particle counts in the fluid entering the hemoperfusion device and that from the fluid leaving the device (Fig. 1.6) (Chang and Malave, 1970). In animal studies blood smear from blood leaving the device did not show any embolic particles. Histological studies in a total of more than 20 dogs did not show any evidence of embolism, even in artificial cell hemoperfusion devices stored for up to one month (Chang and Malave, 1970).

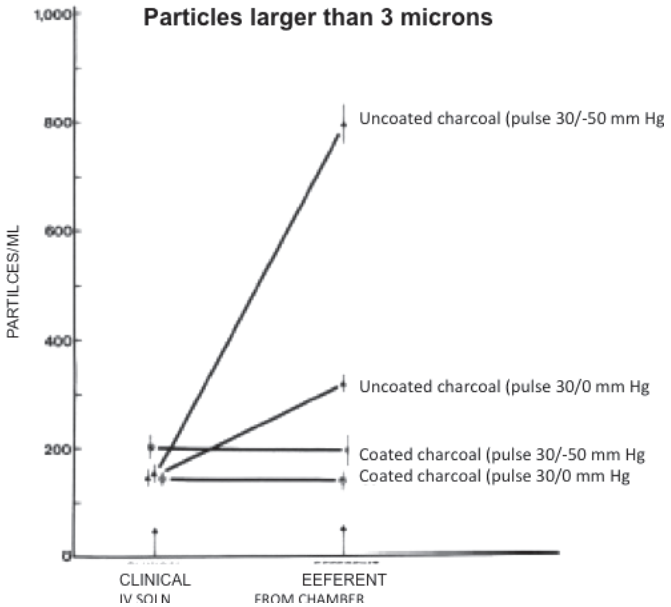


Fig. 1.6. Ultrathin membrane coating modified surface prevents release of particles.

2.6. *Effects of Hemoperfusion on Platelets*

Figure 1.7 shows that uncoated activated charcoal after contact with heparinized blood, when looked at under a scanning electron microscope, shows fibrin entrapment of red blood cells, leukocytes and platelets. On the other hand, the artificial cell in the form of

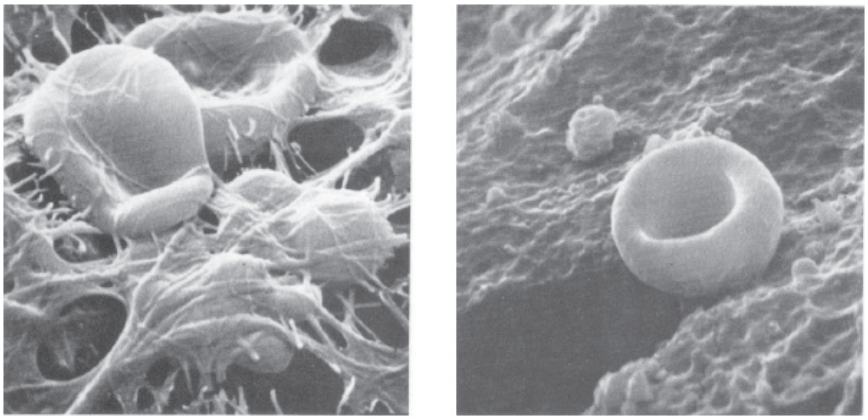


Fig. 1.7. *Left*: Uncoated activated charcoal after contact with heparinized blood looked at under a scanning electron microscope, shows fibrin entrapment of red blood cells, leukocytes and platelets. *Right*: On the other hand, artificial cell in the form of albumin-cellulose nitrate-coated activated charcoal granules did not show fibrin entrapment of formed elements of blood.

albumin-cellulose nitrate-coated activated charcoal granules did not show fibrin entrapment of formed elements of blood (Fig. 1.7) (Chang, 1974b). This scanning electron microscopic study supported the finding that albumin-cellulose nitrate-coated activated charcoal, used both in animal studies (Chang, 1969, 1974b) and in patients (Chang and Malave, 1970; Chang 1974b), prevents the depletion of platelets from the blood. Unlike the 50% decrease in platelet level when using unmodified activated charcoal, platelet levels in patients before and after two hours of hemoperfusion using albumin-cellulose nitrated coated activated charcoal artificial cells remained at 91.8 ± 11.8% (Fig. 1.8). Depending on the blood compatibility of the polymers used for surface modification used by other groups, there can be great variations of down to 50%.

There is no hemolysis or removal of red blood cells by the albumin-cellulose nitrate-coated activated charcoal. Unlike other polymers, cellulose nitrate can bind albumin tightly by adsorption even in the presence of plasma. There were no significant changes in post hemoperfusion plasma hemoglobin levels or leukocyte levels (Chang and Malave, 1974b).

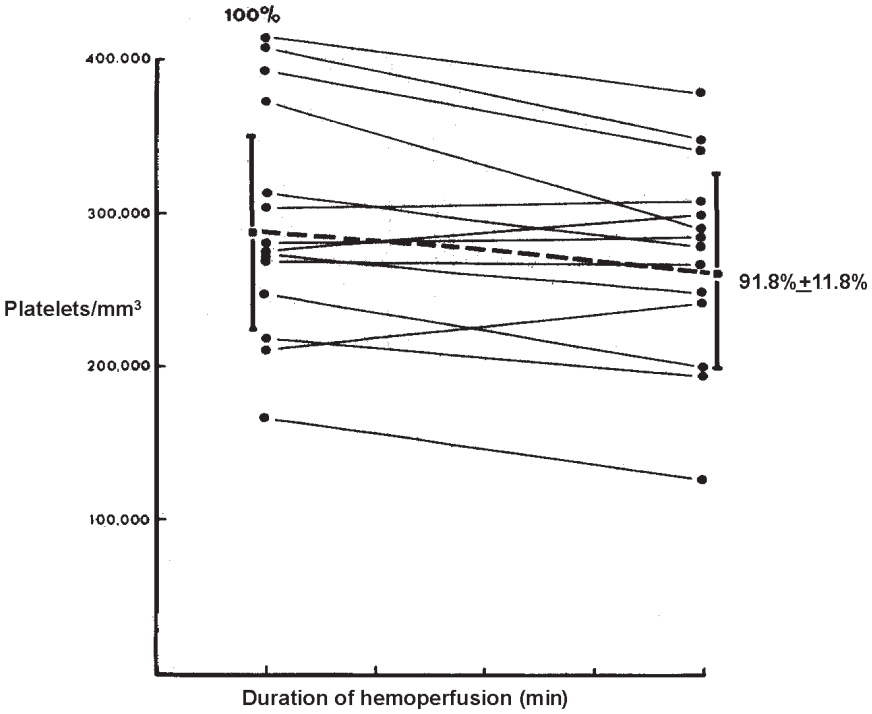


Fig. 1.8. Platelet levels in patients before and after two hours of hemoperfusion using albumin-cellulose nitrated coated activated charcoal artificial cells. There is no significant decrease in platelet level. Earlier report elsewhere using nature activated charcoal without membrane coating resulted in marked decrease in platelet levels.

2.7. *Clearance of the ACAC Artificial Cell Artificial Kidney*

On the basis of the mass transfer analysis (Table 1.1 and Fig. 1.2) one should not be too surprised at the very high clearance value of artificial cells containing activated charcoal (Table 1.3). Activated charcoal adsorbs substances that rapidly cross the membrane. Furthermore, the albumin coating of the artificial cell membrane also takes part in the removal of protein-bound molecules in the circulation (Fig. 1.3). As a result, the clearance for the different metabolites or drugs is many times higher than that for the standard hemodialysis machines.

For instance, as shown in Table 1.3, creatinine clearance is 230 mL/min as compared to 120 mL/min for standard hemodialysis machines.

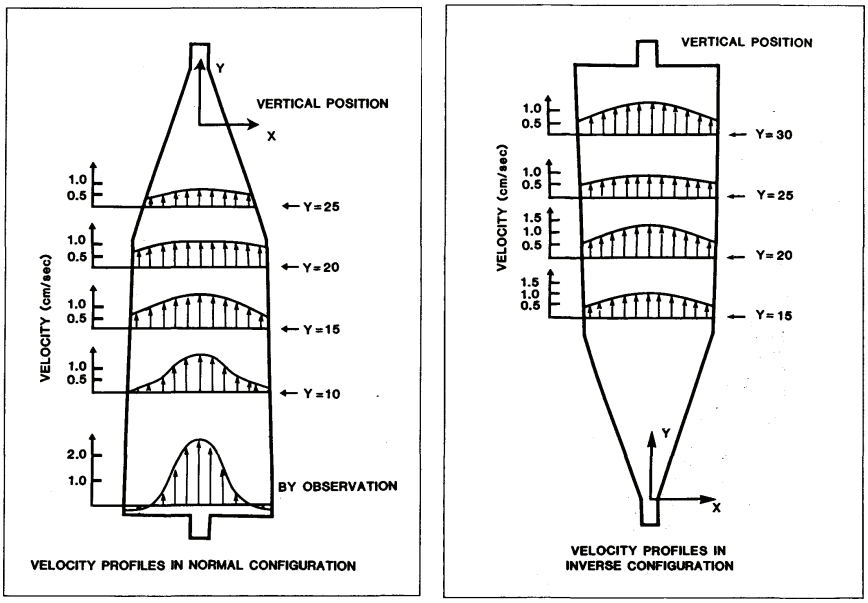
Table 1.3. Clearance ml/min at Blood Flow 300ml/min

	Artificial Kidney HD	Artificial Cell Hemoperfusion
Creatinine	120 mL/min	230 mL/min
Middle molecules	30 mL/min	140 mL/min

What is even more important is the clearance for middle molecules of 140 mL/min as compared to 30 mL/min with the standard hemodialysis machines available up to 1980. The clearance for drugs like phenobarbiturate, methaprylon, methaqualone and glutethimide of between 210 to 230 mL/min is even more striking when compared to the much lower clearance by the standard hemodialysis machines. Clearance for protein-bound molecules, such as glutethimide, is many times higher using artificial cell hemoperfusion. On the other hand, it should be noted that the clearance depends a great deal on the ability of the charcoal to adsorb the material that crosses the artificial cell membrane. Thus, urea and electrolytes are not adsorbed to any extent by the charcoal, and very small clearance is obtained.

2.8. *Improvements in Hydrodynamic*

The laboratory ACAC hemoperfusion device as shown in Fig. 1.5 has configurations and inflow characteristics that allow for good hydrodynamics. However, this configuration is not convenient for industrial scale up. For industrial scale up, the configuration is shown in Fig. 1.9. In this configuration, it is necessary to analyze the optimal hydrodynamics (Victor Chang *et al.*, 1987a). Figure 1.9 shows hydrodynamic measurements of flow with the configuration of the industrial scaled up ACAC hemoperfusion device. When inflow enters the larger end of the device (left figure), there is channeling and stagnation of flow near the wall. This decreases the efficiency of extraction of unwanted molecules from the fluid. Furthermore, this can contribute to deposition of platelets and white cells. When inflow enters the narrow end of the device there is improved flow hydrodynamic with less channeling and less stagnation of flow close to the wall of the device.



(From Victor Chang *et al.*, 1987)

Fig. 1.9. Industrial scaled up ACAC hemoperfusion device. *Left*: Flow pattern when inflow is into the larger end of the device. *Right*: Inflow into the narrow end of the device resulted in improved flow hyrodynamic with less channeling and less stagnation of flow closer to the wall of the device (From V. Chang *et al.*, 1987a).

Table 1.4. Earlier Clinically Used Coated Charcoal Hemoperfusion Devices

Systems	Membrane Material (thickness)
ACAC & CAC (Chang research)	Albumin-collodion or collodion (0.05 μm)
Hemacol (Smith and Nephew)	Acrylic hydrogel (3.0 μm)
Adsorba 300C (Gambro)	Cellulose (3.0 μm)
Nipro Hemocarbo (Nissho)	Collodion (thin)
CAC Dialaid (Montreal, Canada)	Collodion (0.05 μm)
Detoxifier type 1 (Shanghai, China)	Cross-linked gelatin
HNAC (Stefoni, Italy)	Modified acrylic (1.5 μm)
DPH (Kuraray)	Hema-based (0.1 μm?)
Others	

3. Hemoperfusion in Acute Suicidal or Accidental Poisoning

3.1. *Preclinical Studies*

Animal studies in this laboratory showed the effectiveness of this system in the treatment of acute intoxication due to glutethimide, pentobarbital and salicylate (Chang, 1972a). This led to our clinical trials in patients.

3.2. *Criteria for Drug Removal*

It is important to take into consideration the criteria for drug removal by hemoperfusion (Table 1.5). Furthermore, compartmental distribution of a particular drug (Fig. 1.10) should be considered in any clinical use of hemoperfusion.

3.3. *Protocol for Clinical Trials*

Other physicians at that time were not willing to carry out the procedure because of the potential for liability. As a result, I had to prepare the hemoperfusion devices in my laboratory at McGill, bring each of

Table 1.5. Criteria for Drug Removal by Hemoperfusion

1. Permeability of membrane to drug
   (E.g. drugs tightly bound to plasma albumin)
2. Removal after permeation by the adsorbent
   (e.g. highly lipid soluble or protein bound)
4. Removal compared to kidney, liver, GI
5. Time-dose cytotoxic relationship:
   (e.g. If Px delayed theophylline brain damage & paraquat lung damage)
6. Other factors: salicylate (aspirin) removed very efficiently by hemoperfusion but it also causes acidosis that dialysis to adjust acid base balance.

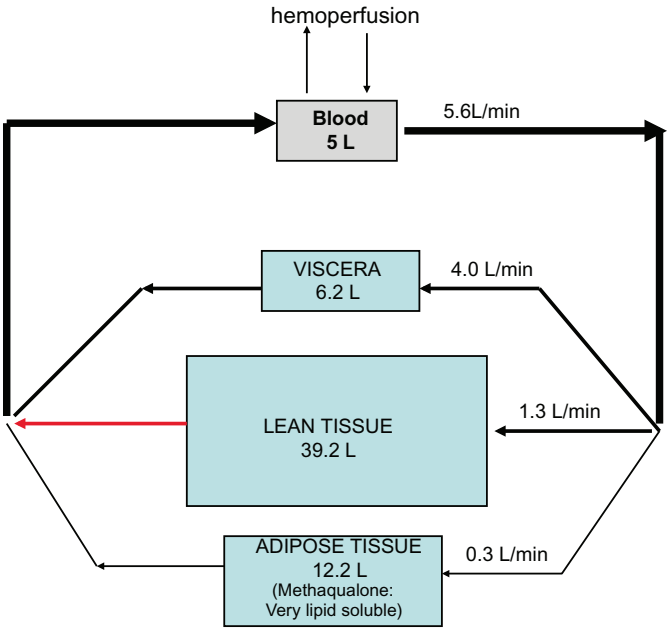


Fig. 1.10. Compartmental distribution of drugs in the body.

them to the hospital and carry out the treatment of the patients myself. The arrangement was for the nephrologists to refer patients to me. I would then make the final decision based on the following criteria (Table 1.5).

For the first three adult patients, I would agree to carry out the procedures only in those patients who were seriously intoxicated with systemic drug level well above the lethal levels or who had serious complications requiring rapid recovery from the effects of the drugs. For example, in one case, before treatment the patient had cardiac arrests on two occasions with possible pulmonary embolism requiring heparinization. Her blood pressure was not obtainable by auscultation and her methyprylon level was twice the lethal level. In this particular case, the desirability of rapid elimination of the drug and its effects is obvious. In another case, a combined intoxication existed — the methyprylon level was three times, and the methaqualone level at least twice the lethal level, furthermore, it is well known that glutethimide is cleared poorly by the standard artificial kidney available at that time. In the case of a pediatric patient with accidental theophylline overdose, irreversible brain damage would have been the result if treatment was not started immediately. In all cases, the potential benefits to the patients had to be high.

3.4. *Result of Clinical Trial on 11 Adult Patients with Suicidal or Accidental Drug Poisoning*

The first three patients are described in more detail (Chang *et al.*, 1973a, 1973b) below to be followed by the other adult patients (Chang 1975g, 1976c, 1980e) and then the pediatric patient.

Case 1: Example of a water-soluble highly permeable and adsorbable drug: A 50-year-old woman, previously treated for depression, was admitted after taking several drugs. She was comatose and her blood pressure was *90/60,* pulse *80/*min. and regular, respiration *12/min.* and temperature 98.4°F. Corneal reflexes were absent. She was treated by intubation followed by gastric lavage containing activated charcoal. Heparin, 5,000 units IV q4h, was started since pulmonary embolism was suspected. Four hr later two cardiac arrests occurred and were reversed with cardiac massage and direct current electroshock. A subsequent chest X-ray showed fracture of four ribs. Ventilatory assistance was required. Standard hemodialysis treatment did not result in any improvement. Ten hr after admission her blood

Table 1.6. First 11 Adult Patients with Suicidal Overdose (Chang *et al.*, 1973a, b; Chang 1975g)

	Clinical Drugs (Coma Grade)		Clearance (ml/min)	Hemoperfusion (Number of 2hr Px)	Outcome
1	IV	Methyprylon	230	2	recovery
2	IV	Glutethimide	150	1	recovery
3	IV	Methyprylon+	230	2	recovery
		Methaqualone	230		
4	IV	Glutethimide	230	4	recovery
5	IV	Phenobarbital	228	1	recovery
6	IV	Phenobarbital	162	1	recovery
7	IV	Glutethimide	—	1	recovery
8	IV	salicylate	150	1	recovery
9	IV	methyprylon	—	1	recovery
10	IV	phencyclidine	—	1	recovery
11	IV	secobarbital	200	1	recovery

pressure could not be determined by auscultation. At this time her blood methyprylon level was 9.4 mg/dL and six hr later it was 9.6 mg/dL. Direct measurement of arterial blood pressure from the A V shunt gave a systolic pressure of 80 mm. Hg (Fig. 1.11).

The patient was referred to me and hemoperfusion was carried out. For the first 20 min the systolic blood pressure was maintained at 90–100 mm Hg with levarterenol. Then the levarterenol was discontinued and the pressure remained at 130–150 mm Hg throughout the three hr of hemoperfusion. The initial arterial blood methyprylon level was 9.6/dL. Hemoperfusion for two hours lowered this to 4.1 mg/dL, which is below the dangerous level of 6 mg/dL (Fig. 1.11). An initial clearance of 250 mL/min was obtained. As a result, the recovery was dramatic and straightforward. For example, voluntary respiration became more regular and increased to *40/min*. with tidal volume increasing to 325 mL during hemoperfusion. Corneal reflexes and voluntary eye opening and blinking returned and response to painful stimuli appeared. Limb movements were detected 27 hr after admission and 4 hr later the patient responded to verbal

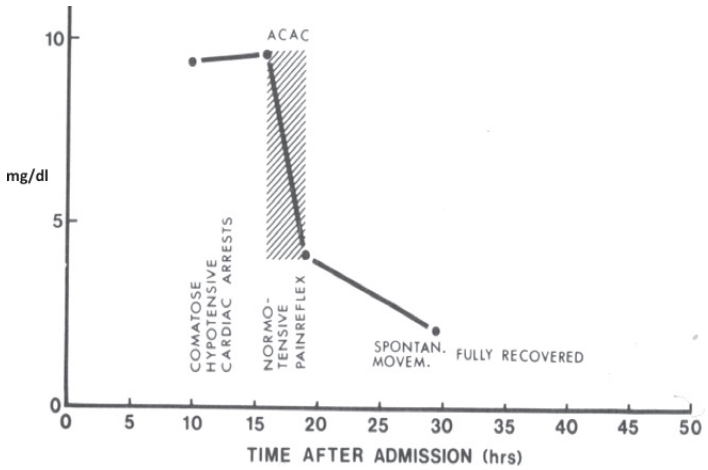


Fig. 1.11. Clinical and laboratory results of hemoperfusion in a patient with severe suicidal methryprylon overdose.

commands. She no longer required ventilatory assistance and started talking four hr later.

Case 2: Example of compartmental distribution of highly lipid-soluble drug: A 26-year-old woman was admitted after ingesting a large amount of glutethimide. She was comatose and areflexic. Her blood pressure was 90/60 and she required ventilatory support. Six hr after admission her systolic blood pressure was less than 70 mm. Hg and isoproterenol was infused. Twenty-four hr after admission her condition was unchanged. Her rectal temperature was 87°F, blood pressure 90/50, and she still required isoproterenol and ventilatory support. At this time she had clinical and X-ray signs of bilateral bronchopneumonia. Her blood glutethimide level was 7 mg/dL. Standard hemodialysis did not result in any improvement.

At 27 hr after admission she was referred to me and treated by hemoperfusion through 300 g of the ACAC microcapsules for two hours. In the course of the hemoperfusion her blood pressure rose from 90/50 to 120/80 in 30 min without isoproterenol infusion. Her blood glutethimide level fell to 3 mg/dL, but 10 hours after completion of the hemoperfusion it rose to 5 mg/dL (Fig. 1.12). Except for

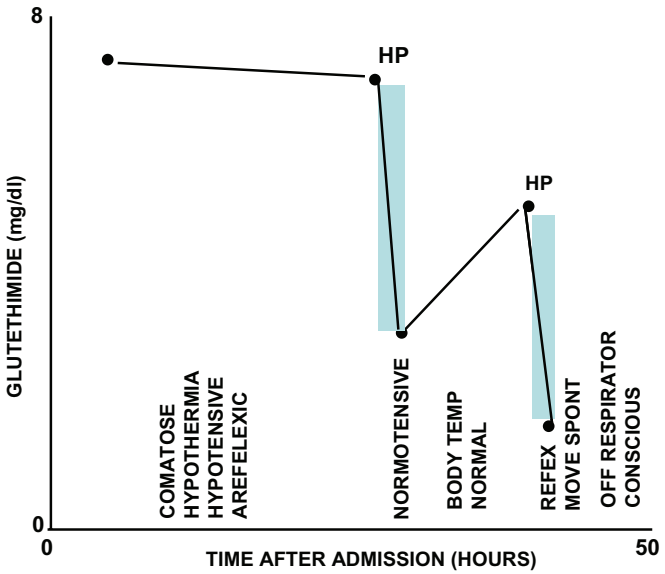


Fig. 1.12. Clinical and laboratory results of hemoperfusion in a patient with severe suicidal glutethimide overdose.

a very slight pupillary reflex and gag reflex, she remained comatose. Her blood pressure was 110/55. Since glutethimide has a high lipid coefficient, a large part of the drug is accumulated in lipoid tissue. The rebound in its level after hemoperfusion likely reflects a redistribution of glutethimide from the lipoid tissue into the bloodstream. A second hemoperfusion with another 300 g of ACAC microcapsules was carried out. Within one hour a 2+ patellar reflex and a slight —plantar reflex could be elicited. After one and one-half hours of hemoperfusion, her tidal volume increased from 250 mL (pretreatment) to 475 mL. In addition, she exhibited some spontaneous limb movements. Her blood pressure increased to 130/75. The posthemoperfusion blood glutethimide level was 1.5 mg/dL (Fig. 1.12). Two hr after completion of the second hemoperfusion she no longer required ventilatory support. She was up and about the following day.

Case 3: A 27-year-old man was admitted after ingesting a mixture of medications. He was comatose and unresponsive to painful stimuli

and required ventilatory assistance. He also showed signs of methaqualone intoxication: tonic convulsions, hypotension, cardiac failure, myoclonia, bleeding tendency, and hypothermia. Gastric lavage was carried out and forced diuresis started. Eight hr after admission his blood methyprylon level was 18.3 mg/dL, three times the "dangerous" level of 6 mg/dL. A 60-min ACAC hemoperfusion was carried out at a blood flow rate of 300 mL/min. The methyprylon level fell to 12.9 mg/dL after the 60-min treatment and by 32 hr after admission was 9.0 mg/dL, lowering its level from three times the dangerous level to just below the dangerous level. Despite this, there was no marked immediate improvement in the patient's clinical condition. At this time we received the laboratory result that the methaqualone level was 6.5 mg/dL, a level that is more than twice the dangerous level of 2.5 mg/dL. A second ACAC hemoperfusion was given over a period of two hr with a blood flow rate of 300 mL/min. The levels fell to 1.8 mg/dL of methyprylon and 2.7 mg/dL of methaqualone. By 48 hr his pupils reacted sluggishly to light, and the gag reflex, deep pain response and bowel sounds were present. At 96 hr his breathing was independent; all reflexes were normal. By 130 hr after admission he was oriented, rational and up and about.

Case 4: This patient was admitted comatose, areflexic, with fixed dilated pupils, and requiring respiratory assist and pressor drug to maintain her blood pressure. She had taken a large mixture of drugs, including glutethimide, thioridazine, salicylate, phenobarbital, and tetracycline, in addition to a large intake of alcohol. She was hemodialyzed three times in the first 48 hr with no change in her condition. She was hemoperfused for 1-1/2 hr with 300 g of ACAC, followed immediately by another 300 g of ACAC hemoperfusion column for 1 hr. With this hemoperfusion her corneal reflex returned and her blood pressure could be maintained without pressor drug. In the next two days she was treated by two hemodialyses but without any changes in her clinical condition. A third hemoperfusion was carried out 10 hr after the last hemodialysis. With this hemoperfusion gag reflex and cough reflex returned and there was occasional spontaneous breathing. This was followed by a fourth hemoperfusion after which spontaneous breathing returned. One day after, she was

responsive and following this she recovered and was up and about. Her phenobarbital level was 20 mg% on admission and clearance obtained was 228.6 mL/min. Her glutethimide clearance obtained was 251 mL/min.

Case 5: A 79-year-old patient was admitted with a history of ingestion of phenobarbital with a blood level of 30 mg%. The patient was comatose, areflexic, and required ventilatory assist when hemoperfusion was carried out. With 2 hr of hemoperfusion, pupil reflex, corneal reflex, and patellar reflex returned. Later the patient started to trigger the respirator, have spontaneous movement and recovered shortly after this. Clearance obtained for hemoperfusion at a blood flow rate of 200 mL/min was 188 mL/min clearance.

Case 6: This patient was admitted with Grade IV coma due to phenobarbital intoxication. The patient received ACAC hemoperfusion at 180–200 mL/min blood flow rate. The clearance was 162 mL/min. Hemoperfusion resulted in recovery of the patient.

Case 7: This 21-year-old patient was admitted with a history of ingestion of glutethimide and phenobarbital. She was admitted in Grade IV coma. There was X-ray evidence of right upper lobe atelectasis and right lower lobe consolidation. One 2 hr hemoperfusion resulted in the improvement of the patient and complete recovery and discharge subsequently.

Case 8: This 22-year-old man was admitted with a history of overdose of salicylate and sodium bromide. The salicylate level was 52.85 mg% when hemoperfusion was started. The clearance obtained at the flow rate of 300 mL/min was 165.9 mL/min. Hemoperfusion of 2 hr lowered the systemic salicylate level to 37.76 mg%. At initiation of hemoperfusion the patient was in Grade II coma responding to painful stimuli. After 1 hr of hemoperfusion the patient recovered consciousness and complained of thirst and hunger and wanted to get up and also carried on conversations. He recovered after this.

Case 9: This was a 51-year-old patient who had taken an overdose of methyprylon. The patient was comatose, areflexic, hypotensive, and on ventilatory assist. The patient received 2 hr of hemoperfusion

with ACAC hemoperfusion at a blood flow rate of 160 mL/min. Two hours after starting hemoperfusion there was bilateral patellar reflex 2+, ankle reflex 2+, light reflex, and some voluntary movement. Shortly afterwards the ventilatory assist was not required and he recovered shortly after this.

Case 10: This was a 30-year-old patient admitted with a history of having taken phencyclidine. Phencyclidine was qualitatively demonstrated in the blood and urine of this patient. The patient was comatose, areflexic, hypotensive, and a 2 hr ACAC hemoperfusion was carried out in this patient. Ater the hemoperfusion the patient still remained comatose. Three days later the patient was off the respiratory and started to have voluntary movement and then recovered after this. In this patient it is not possible to measure phencyclidine level quantitatively to calculate clearance or changes in level because the method available at that time could only give a qualitative assessment of the presence of phencyclidine in blood and urine.

Case 11: This 55-year-old patient was admitted having taken a bottle of Seconal (secobarbital). Shortly after admission he developed respiratory arrest. He was resuscitated, put on a respirator, and blood pressure was maintained with pressor drug. He developed ventricular tachycardia which responded to lidocaine. His secobarbital level was 6 mg%. Two hr of hemoperfusion was carried out. At the beginning the patient was comatose with no reflexes. After 1 hr of hemoperfusion, there was 2+ achilles tendon reflex. And 2 hr after hemoperfusion, both patellar and Achilles reflexes were present. Two days later he recovered completely and was transferred out of the Intensive Care Unit. This hemoperfusion was carried out with the Hemosorba system and the clearance obtained was 200 mL/min.

3.5. *Time–dose Cytotoxicity Relationship: Pediatric Patient with Accidental Theophylline Overdose*

A three-year-10-month female child with a history of asthma developed tachynea, respiratory difficulty and a fever. Instead of pediatric

dose, she was accidentally given the adult dose of 750 mg of theophylline by her family at home, an amount 10 times in excess of that prescribed. She became restless, developed tachycardia, and vomited coffee ground material positive for occult blood. Her serum theophylline level was 67 μg/mL one hour and 45 min after this error. She was admitted to the intensive care unit. The hospital immediately referred this patient to me for possible treatment with ACAC hemoperfusion. It was decided to carry out this procedure immediately because: (1) The theophylline level varied from 67 to 74 μg/mL, with 40 μg/mL being considered a potentially lethal dose. (2) It is known that if the level is not lowered quickly, the child would suffer irreversible brain damage — as in an earlier case when the child was not treated by hemoperfusion. (3) Available dialysis systems at that time were not effective in removing theophylline.

A three-hour hemoperfusion procedure was carried out (Chang *et al.*, 1980a). The maximal blood flow possible in this 15.4 kg child was 60–75mL/min in the first hr. After the first hour, the flow rate could be increased to 90 mL/min, and this rate was maintained for the remainder of the treatment. Before hemoperfusion the child had a tachycardia of 187/min and a blood pressure of 120/70 mm Hg. As hemoperfusion lowered the systemic theophylline level, the heart rate decreased to 145/min at 1 hr, 135/min at two hr and was 127/min at the end of the procedure (Fig. 1.13). Blood pressure was unchanged throughout the hemoperfusion.

Figure 1.13 shows that the blood level of theophylline before HP was 74 μg/mL. Hemoperfusion lowered the level within 1.5 hours to 40 μg/mL and within three hours to 15 μg/mL. Hemoperfusion was discontinued. The theophylline level in the efferent from the hemoperfusion device was zero showing a 100% extract of the drug on one circulation through the device. The removal of the drug from the tissue compartment must also have been high since before hemoperfuion the blood level remained high and stable but after hemoperfusion was completed, the serum level continued to remain at the low level. The child recovered uneventfully.

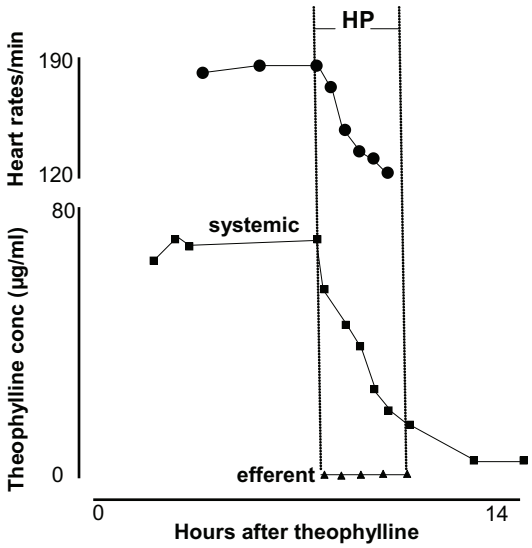


Fig. 1.13. Clinical and laboratory results of hemoperfusion in a three-year-old pediatric patient with severe accidental theophylline overdose. Her level was well above the dangerous level of 40 µg/mL that could have resulted in irreversible brain damage. Hemoperfusion rapidly lowered this level (Chang *et al.*, 1980a).

3.6. *Aluminium–desferal: Solution to Permeation and Adsorbent Problem*

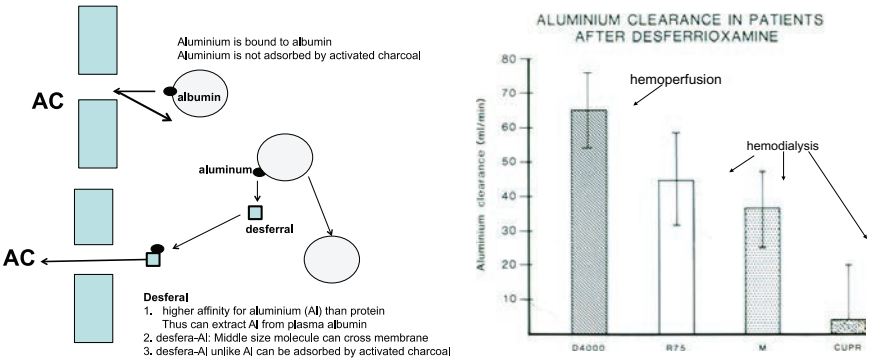


Fig. 1.14. Left: Aluminium is bound to albumin and cannot cross the membrane to be removed by the AC absorbent. With the addition of desferral, aluminium bound to desferral, which is a small molecule that can be adsorbed by AC. As a result the aluminium–desferral complex can cross the membrane to be removed by the AC. Right: Our clinical trial shows that by doing this, aluminium can be more efficiently removed when compared to dialysis (Chang and Barre, 1983, *Lancet*).

3.7. *Routine Clinical Uses in Patients Around the World*

Activated charcoal is a well-known adsorbent for a large number of drugs and toxins. Artificial cells containing activated charcoal, as demonstrated here, take advantage of this adsorbing property and at the same time prevent the two major problems of charcoal embolism and reduction in platelets. The results of these first clinical trials have led to the use of this approach around the world for the treatment of patients with accidental or suicidal poisoning (Better *et al.*, 1979; Biberstein *et al.*, 1983; Cohan *et al.*, 1982; Verpooten *et al.*, 1984; Gelfand *et al.*, 1977; Gibson *et al.*, 1978; Lorch and Garella, 1979; Winchester, 1996; Diaz-Buxo *et al.*, 1978; Sideman and Chang, 1980b; Piskin and Chang, 1982; Chang and Zheng, 1983; Chang and Ho, 1985; Chang and Nicolaev, 1987; Chang and Odaka, 1991; Klinmann *et al.*, 1990; Chang and Odaka, 1991; Kawasaki, 2000; Lin *et al.*, 2002; Lopez-Lago *et al.,* 2002; Peng *et al.*, 2004, Chinese symposium in hemoperfusion, 2005). More recent results are available in chapters in the present book.

The exact methods of preparation of artificial cells containing activated charcoal have been published in reproducible detail for all to use (Chang, 1972a). As a result, a number of countries started to produce their own industrial hemoperfusion devices. As would be expected, there are variations and extension of Chang's original method resulting in variations in efficacy and biocompatibility. While the inferior ones are no longer in use, those that are safe and effective are being used in routine clinical treatment of accidental and suicidal poisoning. In some areas of the world, for some unknown reasons, these devices are extremely expensive and as a result are too costly for wide spread use. In other areas of the world, especially where hemodialysis machines are not easily accessible, inexpensive but safe and efficient devices are being produced and used extensively. All the very extensive experience in the use of adsorbent artificial cells in hemoperfusion for acute poisoning has led the nephrologists to establish the following criteria for using this in acute poisoning (Table 1.7).

Table 1.7. Clinical Criteria for Hemoperfusion (modified from Winchester, 1996)

1. Progressive deterioration despite intensive care.
2. Severe intoxication with mid-brain dysfunction.
3. Development of complications of coma.
4. Impairment of normal drug excretory function.
5. Intoxication with agents producing metabolic and/or delayed effects.
6. Intoxication with an extractable drug that can be removed at a greater rate than endogenous elimination

Because of its efficient adsorbing properties for numerous drugs the system may be even more useful in cases of acute intoxication involving a number of drugs, especially when the exact drugs are not known at the time that treatment is required. Being portable and having a constant extracorporeal volume, it is particularly useful in areas where hemodialysis machines are not easily accessible or in pediatric practice.

4. Hemoperfusion in Terminal Renal Failure Patients

4.1. *Rationales*

Hemodialysis machines are effective in the treatment of chronic renal failure patients. However, at that time there were not enough machines; furthermore it was extremely expensive. Only a small number of patients can receive treatment in a few countries. In most other countries, the high cost and unavailability of machines prevented the use of this in terminal renal failure patients. Since hemoperfusion is efficient in removing toxin or unwanted waste from the blood, we carried out study into its possible use in uremic patients.

This author has carried out 55 hemoperfusion procedures in 14 renal failure patients. Initially, only one hemoperfusion procedure was carried out on each of four terminal renal failure patients. Having

shown the safety of this procedure, two hemoperfusions were carried out on the fifth patient and three procedures were then carried out on each of the next three patients. After this, a 72-year-old woman, who could not be managed by peritoneal dialysis or hemodialysis, was placed on an eight-month regime of hemoperfusions supplemented with hemodialysis as required, the latter for the removal of urea, water, and electrolytes. Long-term hemoperfusion in this patient was safe and effective, and her condition was stabilized sufficiently for her to be maintained on standard dialysis for the next 10 years. This led to the inclusion of other patients for long-term hemoperfusion.

Since commercial devices were not available until later, the total number of patients was limited by my having to prepare the devices myself and also to carry out the procedure at that time. To allow for objective clinical assessment, I was responsible for the preparation of the hemoperfusion device and the carrying out of the procedures on patients. A group of nephrologists would refer the patients and independently assess the clinical and laboratory results. The patients were otherwise treated as any other hemodialysis patient in the McGill teaching hospital dialysis units, where medications, frequencies of transfusions, and number of supplemental hemodialyses were determined independently by the nephrologists. The standard chronic hemodialysis program at that time was for each patient to receive an average of two 6 h hemodialyses each week, usually on the EX 01 hemodialyzer.

4.2. *Hemoperfusion Alone Supplemented by Hemodialysis*

General clinical results

No adverse effects from hemoperfusions were observed in the patients. There was little or no change in blood pressure throughout the hemoperfusion procedure, even in patients who normally experienced severe hypotensive episodes when on the EX 01 hemodialyzers.

Immediately after the 2 hr hemoperfusion, the patients feel much less fatigued than when they undergo the 6 hr hemodialysis with the EX 01 artificial kidney. This is especially so in a patient who normally stays home in the evening to rest after the 6 hr EX 01 hemodialysis treatment. In contrast, 1 hr after the 2 hr ACAC hemoperfusion, she goes out to have dinner, make social visits or go to the theater. At the initiation of the clinical trial, each patient receiving hemoperfusion is required to stay in the hospital overnight for observation before being allowed to return home the next day. When the procedure is found to be safe, patients treated with the hemoperfusion procedure are allowed to go home 1 hr after hemoperfusion. The patients' general well being is at least as good on the weekly 2 hr ACAC hemoperfusion and 6 hr hemodialysis (EX 01) as on the twice-weekly 6 hr EX 01 hemodialysis. The following are examples of patients on longer term treatment with hemoperfusion.

First patient on long-term hemoperfusion

This is a 72-year-old woman with chronic renal failure and congestive heart failure. She was admitted with complaints of nausea, vomiting, low back pain, diarrhea and hiccups. She was bedridden in the hospital, with a BUN of 186 mg/dL, creatinine of 24 mg/dL, and a 24 hr creatinine excretion of 80 mg. She was placed on peritoneal dialysis, but this resulted in massive intra-abdominal bleeding and severe shock. Hemodialysis treatment resulted in hypotension. She was referred to this author since there was no other way to treat her condition. At that time, because of lack of facilities, patients of her age were not generally accepted into a long-term hemodialysis program. Thus, I first had the dialysis unit agree that if she improved on the hemoperfusion program, the dialysis unit would accept her on the standard dialysis program. For the next 50 days, she was treated with nine hemoperfusion procedures each lasting for 2 hr. During these 50 days she received only one hemodialysis for the removal of water and electrolytes. After this she continued for a total of eight months on hemoperfusion combined with hemodialysis. The schedule of

treatment and response for the first 50 days of her eight-month treatment on hemoperfusion are summarized in Fig. 1.15.

On this regime, her uremic symptoms of nausea, vomiting, diarrhea and hiccups cleared. Surprisingly, after two weeks on this regime, she felt well enough to be allowed by the nephrologists to leave the hospital and return home to her husband. During this time, she no longer had uremic symptoms and was able to do her shopping and housework. At the beginning she was asked to stay in the hospital for 24 hr after each procedure. Later, she only came to the hospital 1 hr before her hemoperfusion and then returned home 1 hr after the completion of the hemoperfusion. There were no side effects throughout all her hemoperfusions. There was little or no change in her blood pressure, nor other clinical side effects. This is contrary to her standard hemodialysis treatment with the EX 01, where she had

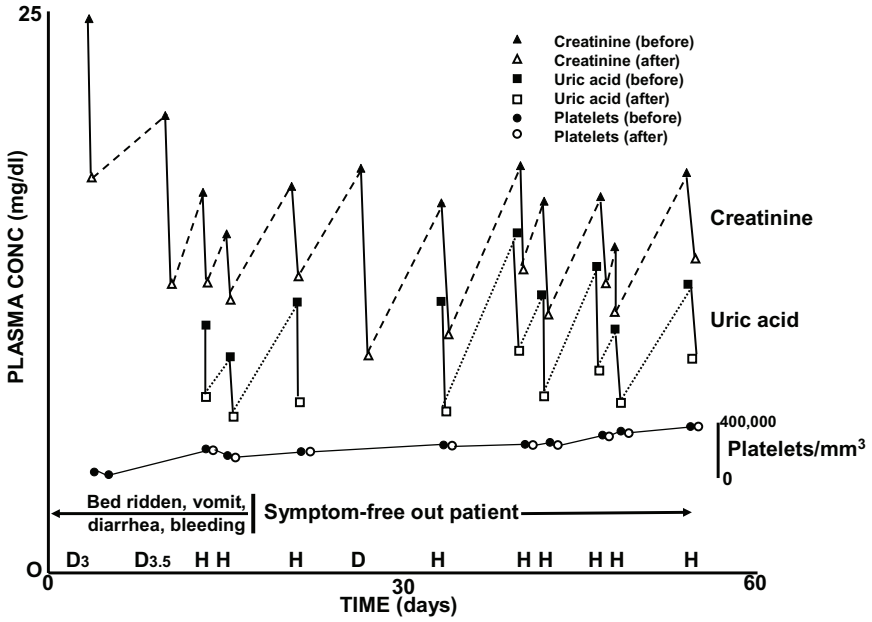


Fig. 1.15. First terminal renal failure patient on long-term hemoperfusion.
Graph shows the results of the first 50 days of the eight-month treatment.

hypotensive episodes with hemodialysis especially during fluid removal.

After the 50-day period, the dialysis unit admitted her on a half time basis with one 6 hr hemodialysis per week, with a 2 hr hemoperfusion per week. During the eight-month period, she received a total of 24 hemoperfusion procedures and all were uneventful with no side effects. The only problem was fluid retention since hemoperfusion does not remove fluid. After a total of eight months on the hemoperfusion program, she was placed on a standard two-weekly 6 hr hemodialysis program for the next 10 years until she passed away at over 80 years of age. Independent inquiry by the nephrologists showed that her feeling of well-being was the same when she was on an average weekly regime of 2 hr hemoperfusion plus 6 hr hemodialysis as compared to her twice-a-week 6 hr hemodialysis. Thus 2 hr on hemoperfusion seems to be as effective as 6 hr of hemodialysis.

A 51-year-old woman was admitted with a long history of hypertension and chronic renal failure caused by chronic pyelonephritis. Her urine output remains at about 500 mL/day with creatinine excretion of 0.4 g/24 hr. She was started on occasional peritoneal dialysis and then on 6 hr twice-weekly EX 01 hemodialysis while waiting for renal transplantation. She developed severe pruritis which disturbed her sleep at night and was a nuisance in the daytime. Because of this, she was started on hemoperfusion to treat her pruritis. She continued on the 6 hr twice-weekly hemodialysis program with the addition of a 2 hr weekly hemoperfusion. This treatment resulted in a marked decrease of her pruritis. In addition, her acceptance of the hemoperfusion procedure was such that she was placed on the long-term hemoperfusion regime of one 2 hr hemoperfusion plus one 6 hr EX 01 hemodialysis weekly. In addition to her diminished pruritis, she found that with hemoperfusion she could come in 1 hr before hemoperfusion, have 2 hr ACAC hemoperfusion, and after the treatment, feel well enough to go directly to social evenings, dancing, or playing cards with her friends. On the other hand, with EX 01 hemodialysis she felt tired and had to rest at home in the evening. Furthermore, she experienced cramps in her legs during or soon after each 6 hr EX 01 hemodialysis. She remained symptom

free and with no pruritis on this hemoperfusion and hemodialysis program for four months. After this, she returned to the standard hemodialysis program because one hemodialysis each week was not enough to control her body fluid.

A 53-year-old male with chronic renal failure was started on the 6 hr twice-weekly EX 01 hemodialysis. His daily urine output was 1L and creatinine excretion was 0.5 g. He was started on a weekly 2 hr hemoperfusion and 6 hr EX 01 hemodialysis program. Being a very active business man, he accepted this program because it meant that on the day of treatment with hemoperfusion, he could work in the morning, have his lunch and come in for treatment then return in the same afternoon, sometimes to work further in the evening. At the end of three weeks he received a renal transplant.

A 21-year-old man was admitted to the hospital with symptoms of cramps, headaches, nausea, vomiting and diarrhea. His creatinine clearance was 1.6 mL/min and urinary output was 700 mL/day. This patient, with spina bifida at birth, was paraplegic with a neurogenic bladder, recurring urinary tract infection and acute pyelonephritis. At that time, there was no opening for him in the chronic hemodialysis program, and he was not considered suitable for renal transplantation. The patient was treated with 2 hr of hemoperfusion weekly, supplemented by very occasional hemodialysis as needed for control of fluid and electrolytes. This treatment resulted in marked improvement of the patient's symptoms — except for occasional diarrhea. He was well enough to return to work. Three months later, an opening became available in the chronic hemodialysis unit and the patient was treated with an average of once a week 2 hr hemoperfusion plus once a week 6 hr hemodialysis. After a total of six months on hemoperfusion, the patient continued to be symptom free. There was improvement in nerve conduction velocity. Each 2 hr hemoperfusion lowered the serum middle molecule (300–1500 mol wt) level by 55%. He functioned well and was able to work and swim. The only problem was that one hemodialysis per week was not enough to prevent fluid retention. Thus, after six months on this program he was placed on the standard twice a week hemodialysis program.

4.3. *Hemoperfusion and Removal of Uremic Metabolites*

Since then other artificial-cell-based hemoperfusion devices have been produced industrially. The following table (Table 1.8) shows that the better hemoperfusion devices are much more effective than the dialysers available at that time for the removal of uremic metabolites as shown by the clearance for creatinine, uric acid and middle molecules. Also, with the better hemoperfusion systems like ACAC and Adsorba 300C, there was no significant effect on the platelet levels.

It has been strongly proposed that middle molecular weight substances (300–5,000 m.w.) including ß-2-microglobulin (11,800 m.w.), may be responsible for uremic symptoms. However, the hemodialysis membrane available at that time had a very low clearance for middle molecules and required up to eight hours for effective removal. On the other hand, the better hemoperfusion devices are much more efficient in removing middle molecules (Table 1.8; Fig. 1.6) (Chang, 1972e; Chang and Migchelsen, 1973; Chang and Lister, 1980, 1981).

4.4. *Conjoint Hemoperfusion-Hemodialysis*

The above result shows that hemoperfusion is able to carry out its function in removing toxin or unwanted waste metabolite to keep patients symptom free (Table 1.9). On the other hand, the above clinical results also showed that hemoperfusion, even with occasional hemodialysis, cannot look after electrolytes or fluid retention. For the these reasons, clinical investigators around the world started to carry out clinical trials using hemoperfusion in series with hemodialysis for patients with dialysis-resistant uremic symptoms and also to reduce the time needed for treatment (Chang *et al.*, 1975, 1982b; Martin *et al.*, 1979; Inou *et al.*, 1979; Odaka *et al.*, 1980; Agishi *et al.*, 1980; Stefoni *et al.*, 1980, others in this book). The use of the better commercially prepared hemoperfusion devices in series with hemodialysers resulted in clinical improvements in "well-being," nerve conduction velocity, pruritis, pericarditis, peripheral neuropathy and, what is also important, reduction in treatment time (Table 1.9) (Chang *et al.*, 1975, 1982b; Martin *et al.*, 1979; Inou *et al.*, 1979; Odaka *et al.*, 1980;

Table 1.8. Characteristic of Artificial-Cell-Based Hemoperfusion Devices

	ACAC	Hemacol	Adsorba 300C
Hemoperfusion system	Albumin collodion coated (300 g) (0.05–0.5 micron)	Acrylic hydrogel coated (300 g) (3–5 micron)	Cellulose acetate coated (300 g) (3–5 micron)
Max. clearance (ml/min)			
creatinine	235 (QB 300)	181 (QB 300)	185 (QB 200)
uric acid	230 (QB 300)	116 (QB 300)	186 (QB 200)
middle molecules			
300–1500	144 (QB 300)	as in dialyzer	no data
1000–2000 (peak 7c)	no data	no data	120 (QB 300)
2000–5000	93 (QB 300)	no data	no data
PTH (free)			
% of pre-perfusion platelet level	92–100%	70–80%	90–100%
References	Chang *et al.* Odaka *et al.*	Winchester *et al.*	Martin *et al.* Oulès *et al.*

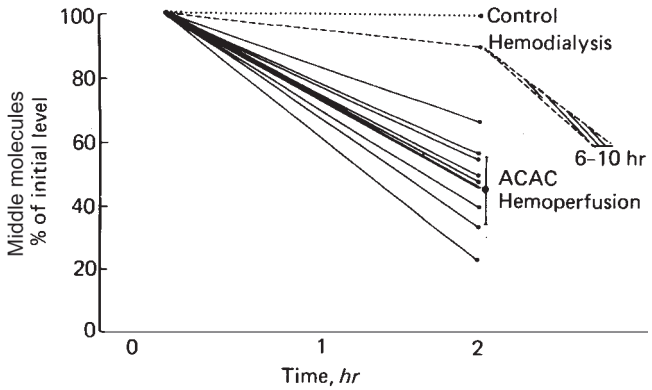


Fig. 1.16. Clinical studies in uremic patients show that middle molecules can be lowered rapidly after two hours of ACAC hemoperfusion. On the other hand, hemodialysis machines available at that time were not effective.

Table 1.9. Effects of Hemoperfusion in Uremic Patients

Authors	Clinical Improvements in the Following Symptoms
Chang *et al.*, 1971–1974	Pruritis, well-being, nausea, vomiting
Chang *et al.*, 1975	Peripheral neuropathy
Odaka *et al.*, 1978	Pericarditis, symptom free
Chang *et al.*, 1979	Hematocrit, less fluid retention
Martin *et al.*, 1979	Pericarditis
Inou *et al.*, 1979	Peripheral neuropathy
Odaka *et al.*, 1980	Pericarditis
Agishi *et al.*, 1980	Peripheral neuropathy
Stefoni *et al.*, 1980	Peripheral neuropathy, pruritis, pericarditis, well-being

Agishi *et al.*, 1980; Stefoni *et al.*, 1980, others in this book). These clinical trial results led many centers to use the combined hemoperfusion-hemodialysis, especially in those patients with resistant uremic symptoms under the standard hemodialysis program.

We designed a device, Dialaid D4000, combining hemoperfusion in series with a capillary membrane system (Fig. 1.17, Table 1.10) to carry out both functions (Chang *et al.*, 1982a and 1982b).

Since then, hemodialysis membranes have improved so that the present high flux membranes are better than the standard dialysis membrane in removing the larger middle molecules. Even then, the clearance is still much less than for the better hemoperfusion devices. Hemoperfusion devices are usually manufactured by manufacturers of hemodialysis machines and dialysis membranes. In those countries with strong hemodialysis companies, the hemoperfusion devices are extremely expensive. On the other hand, in those countries with no large dialysis industries, hemoperfusion devices are not expensive and therefore continue to be used for renal failure patients. More recent results are available in this book. In all countries, hemoperfusion continues to be commonly used for uremic patients with aluminium or iron overload. This is based on the earlier clinical demonstration of

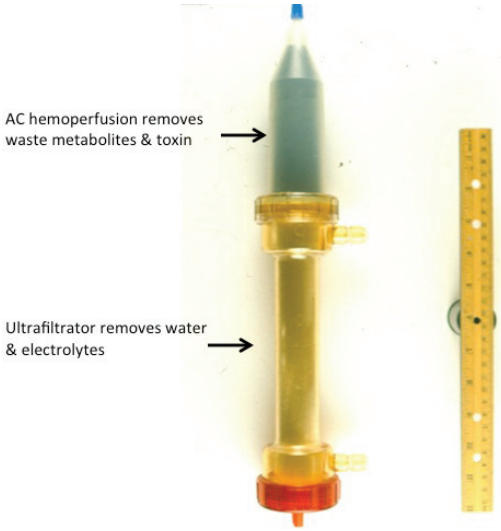


Fig. 1.17. Dialaid D4000 combining hemoperfusion (upper section) with a capillary membrane system for dialysis (lower section).

Table 1.10. Clinical Result

	Clearance (mL/min)	Pre CAK	2 1/2 HR CAK
Middle Molecules (peak 7)	165.2 ± 1735	40.8 ± 8.04	16.16 ± 7.18
Creatinine (μM/L)	194.0 ± 26.5	1519 ± 231	792 ± 192
Uric Acid (μM/L)	167.9 ± 22.2	589 ± 97	276 ± 66
Urea (μM/L)	142.5 ± 20.4	31.0 ± 11.9	16.9 ± 6.6
Phosphate (μM/L)	112.3 ± 34.6	1.7 ± 0.4	1.0 ± 0.3
Platelet ($\times 10^3$)		312 ± 54	265 ± 57 (n.s.)
Leucocytes ($\times 10^3$)		7.4 ± 1.0	7.9 ± 1.2 (n.s.)
Neutrophil (z)		82.3 ± 6.7	82.6 ± 7.9 (n.s.)
Lymphocytes (z)		13.9 ± 4.3	13.7 ± 6.6 (n.s.)
RBC ($\times 10^6$)		3.5 ± 0.7	4.0 ± 1.0 (n.s.)

the use of deferoxamine to bind these heavy metals and for hemoperfusion to remove the complex (Fig. 1.14) (Chang and Barre, 1983; Chang, 1986d; Chang *et al.*, 1984a, 1989a; Hakim *et al.*, 1985; Winchester 1996).

4.5. *Miniaturized Artificial Kidney-based on Hemoperfusion-ultrafiltration*

A third approach is to construct a truly miniaturized artificial kidney based on hemoperfusion in series with an small ultrafiltrator (Chang *et al.*, 1975, 1979a, 1977b; Chang, 1976c) (Fig. 1.18). In clinical studies, a small Amicon ultratiltrator was used (Fig. 18). Hydrostatic pressure from the blood pump alone gave effective ultrafiltration. Dialysis fluid is not required; the ultrafiltrate flows directly into a measuring cylinder.

This ultrafiltrator in series with ACAC hemoperfusion was studied in two patients, one for three and the other for six months (Chang *et al.*, 1979). The patient treated for six months has a creatinine clearance of 0.2 mL/min and a urine volume of 50 mL/day. He was followed for a six-month control period of thrice weekly hemodialysis treatments. This was followed by a six-month test period when a 2.5 hr hemoperfusion-ultrafiltration replaced one of the three weekly 6 hr hemodialysis treatments (Table 1.11, Fig. 1.19).

The patient felt well throughout. Hematocrit increased slightly from 25.15% ± 3.61 to 26.6% ± 1.73. Fluid retention diminished as body weight fell from 82.6 ± 1.2 to the optimal dry weight of 78.0 ± 0.8 kg and hypertension improved. More fluid could be removed without side effects in 2.5 hr of hemoperfusion-ultrafiltration than that by 6.0 hr of hemodialysis. Middle molecule clearance in this patient was 113 mL/min at a blood flow rate (QB) of 200 and 160 mL/min at QB of 300. This was significantly higher than for hemodialysis. Nerve conduction velocity did not change. Hemoperfusion-ultrafiltration is more effective than hemodialysis in removing middle molecules, creatinine, uric acid, sodium chloride and water (Table 1.11). On the other hand, it does not remove

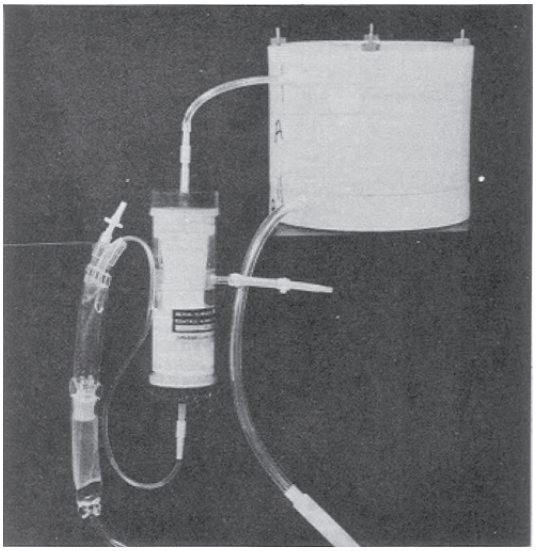


Fig. 1.18. ACAC hemoperfusion in series with a small ultrafiltrator.
Promising clinical results led us to modify the D4000 so that it has a ultrafiltrator in series with the hemoperfusion.

Table 1.11. Patient on Hemoperfusion-Ultrafiltraion (Creatinine Clearance: 0.2 mL/min; Urine Output: 50 mL/24 hr)

Clearance (mL/min) (at QB 300 mL/min)	Hemoperfusion	Hemoperfusion-Ultrafiltration
Creatinine	230	235
Uric acid	235	235
300–1500 MW	120	134
PTH free	73	81
Fluid removal/2hr	0	2,500–2,700 mL
NaCl removal/2hr	0	17.0–18.4 g

sufficient potassium and urea since after six months on this regime, there was an increase in mean blood urea nitrogen from 86 ± 14 to 105 ± 18 mg/dL and potassium from 5.2 ± 0.57 to 5.8 ± 0.08 mEq/L. Oral adsorbents can remove potassium and phosphate.

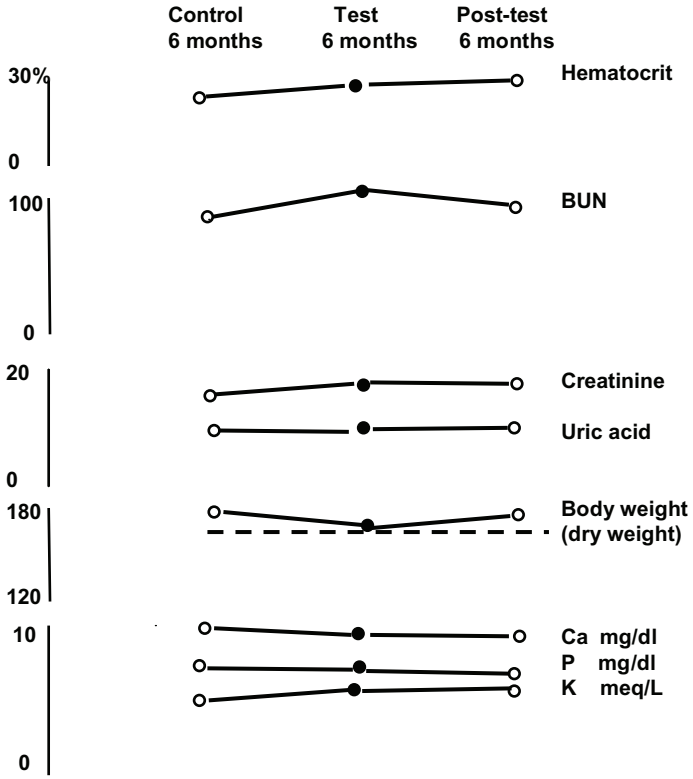


Fig. 1.19. Laboratory data of patient. A six-month control period followed by a six-month test period. During the test period, one of the weekly six-hour hemodialysis treatments was replaced by 2.5 hours of treatment using the miniaturized hemoperfusion-ultrafiltration device.

4.6. *Urea Removal Systems*

A urea removal system is being developed to complete this miniaturized artificial kidney system. This is based on the finding that artificial cells containing the enzyme urease can convert urea into ammonia that is then removed by ammonia adsorbent (Chang, 1966). This was developed and tested in patients (Kjellstrand *et al.*, 1981). However, too much ammonium adsorbent was needed. In order to solve this problem, artificial cells containing multi-enzyme systems were studied (Gu and Chang, 1988a, 1988b, 1990a, 1990b, 1990c, 1991).

Another approach is the use of artificial cells containing urea-removing microorganisms (Prakash and Chang, 1996, 1998, 1999, 2000a, 2000b) including our use of artificial cells containing modified *lactobacillus* (Chow, Liu, Prakash, Chang, 2003). *Lactobacillus* is commonly used in yogurt for human consumption. Professor Friedman's group has extended this and tested clinically in patients with promising results (Friedman, 2011).

5. Hemoperfusion in Liver Failure

5.1. *First Observation of Recovery of Consciousness in Hepatic Coma*

As shown in acute poisoning patients in the above section, adsorbent artificial cell hemoperfusion is effective in removing suicidal and accidental overdoses of medications in patients. It is also effective in removing other toxic substances from the circulating blood. Its effectiveness in removing hepatic toxins from the circulating blood was first shown in a grade IV hepatic coma patient with recovery of consciousness within an hour after the initiation of hemoperfusion (Chang, 1972b).

A 50-year-old woman was admitted with a history of alcoholic abuse, onset of jaundice, fatigue, nausea, vomiting, and dark urine. There was no history of contact with hepatitis or of intravenous or intramuscular medication. On admission, she had spider nevi and ascites. The diagnosis was acute alcoholic hepatitis. Her condition deteriorated after admission and she became comatose and unresponsive. After she remained comatose for two days, her condition was considered as terminal, and with the insistence of her relatives she was referred by her physician to me for possible hemoperfusion since nothing else could be done. One hour after hemoperfusion her consciousness started to improve, and she began to recognize her relative and answer questions in sentences. Hemoperfusion was carried out for a total of 80 minutes. She remained conscious for about an hour after the end of the hemoperfusion, but lapsed into coma again.

Three days later she was still comatose, and a second hemoperfusion was initiated. At the start of perfusion she was comatose, an hour later she looked at people when spoken to and there were increases in voluntary movements and response to pain. She did not, however, recover full consciousness as in the first hemoperfusion. Shortly after this a liver biopsy specimen showed cirrhosis, acute hepatitis, with small foci of regeneration. Thereafter consciousness fluctuated between stupor and coma. A third hemoperfusion was carried out. Before this hemoperfusion, E.E.G. background activity was irregular and diffuse, with continuous theta and delta activity and occasional high-amplitude single slow-wave and rare complex biphasic or triphasic configurations. At this time the patient was semi-comatose and did not respond to questions. An hour and a half after hemoperfusion the patient's consciousness improved and she started to respond and answer questions; she also complained of thirst and heaviness in the leg. E.E.G. recording after hemoperfusion showed a minimum improvement in the background activity.

Biochemical evaluation of the treatment of hepatic coma is difficult, because the precise pathological mechanism is not known. On the other band, the three hemoperfusions each produced a clinical response in consciousness. In one case when the E.E.G. was recorded there was a slight improvement in background activity. Since there was no change in the blood-ammonia level after hemoperfusion, we cannot attribute the improvement in consciousness to the removal of blood-ammonia. However, whereas standard hemodialysers at that time were not efficient in removing large molecules from blood, hemoperfusion is very efficient in removing molecules up to 5,000 molecular weight (Chang, 1972e, Chang and Migchelsen, 1973; Chang and Lister, 1980, 1981) and also protein-bound molecules. Hemoperfusion is also effective in removing other chemicals related to hepatic coma.

5.2. *Results around the World on Effect of Hemoperfusion on Hepatic Coma*

This led to further studies around the world in a large number of patients (Gazzard *et al.*, 1974; Chang, 1976c, 1982a; Blume *et al.*,

1976; Bartels *et al.*, 1977, 1981; Silk and Williams, 1978; Gelfand *et al.*, 1978, Gimson *et al.*, 1978; Odaka *et al.*, 1978; Amano *et al.*, 1978; Maeda *et al.*, 1980; Cordoatri *et al.*, 1982; William, 1983; O'Grady *et al.*, 1988, others in this book). These results support the finding that a significant number of hepatic coma patients recovered consciousness. However, this did not translated into improved survival rate. Furthermore, these clinical results are not conclusive since the pathogenesis of hepatic coma and survival rate is complicated. In addition to hepatic toxins other factors like brain edema, standard of care also play important roles (William, 1983; O'Grady *et al.*, 1988). Furthermore, survival rate is related to age, etiology, grades of coma, and other complications, especially brain edema. In addition, hemoperfusion can only remove toxins from the body, but the liver is a very complex organ with many other metabolic and synthetic functions. We should not expect hemoperfusion alone to be a complete artificial liver. Hemoperfusion will more likely be an important component of a more complex system (Chang, 1983a, 1983e, 1986c, 1992b).

5.3. *Control Studies in Galactosamine-induced Hepatic Failure Rats*

We therefore carried out detailed control studies in galactosamine-induced hepatic failure rats to allow for a more valid statistical analysis (Chang *et al.*, 1978; Chang, 1971a, 1978b; Chirito *et al.*, 1978, 1979; Mohsini *et al.*, 1980; Tabata and Chang, 1980). With this model we can avoid variations in age, etiology and grades of coma. However, this model may not be the counterpart of fulminant hepatic failure in human. In addition the survival rate in this model of grade III coma is more like grade IV coma in human. This research included detailed studies in regard to the time of initiation of treatment; the need for supplements of essential factors; comparison of hemoperfusion with exchange transfusion, liver perfusion, and hormones; and other approaches. Male Wistar rats weighing 275–309 g and 47–67 days old were used. Forty-eight hr after galactosamine injection (1.1 g/kg), those rats in Grade III coma were used in this study. Grade III coma rats were those which "sleep most of the time,

but arousable." Of the 356 rats, 122 reached Grade III coma 48 h after injection with galactosamine. To avoid variations between batches, all the animals in Grade III coma in each batch were randomly divided into equal numbers of test and control animals. Similar studies were also carried out in rats in grade II coma. The results of all the studies (Chang *et al.*, 1978; Mohsini *et al.*, 1980; Tabata and Chang, 1980) are very briefly summarized in Table 1.12.

In grade II coma rats, either one hemoperfusion or one liver perfusion resulted in significant increase in survival time and survival rates when compared to the control group (Table 1.12). However, cross circulation did not have any significant effects.

In grade III coma rats, one of hemoperfusion, liver perfusion or blood exchange transfusion did not result in any significant increase in survival time or survival rates. On the other hand, combined use of one hemoperfusion with one blood exchange transfusion resulted in significant increase in survival time but not survival rate. Two hemoperfusions also resulted in significant increase in survival time but not survival rate (Table 1.12). Another approach was carried out with two hemoperfusions after one blood exchange, with the second hemoperfusion 4 h after the first. When this regime was used, both the survival time and the survival rate of Grade III coma rats were significantly increased ($p < 0.01$ and $p < 0.05$, respectively) (Table 1.12).

Table 1.12. Survival Time and Rates and Grades of Coma in Rats Treated by Hemoperfusion (ACAC) Alone or in Combination

Coma	Treatment	Survival Time	Survival Rate
II	ACAC hemoperfusion	↑	↑
II	Liver perfusion	↑	↑
II	Cross-circulation	NS	NS
III	ACAC hemoperfusion		NS
III	Liver perfusion	NS	NS
III	Blood exchange	NS	NS
III	Blood exchange + ACAC	↑	NS
III	ACAC + glucagon + insulin	NS	NS
III	2 × ACAC + Blood exchange	↑	↑

Our research in fulminant hepatic rat models shows that hemoperfusion started in the earlier grades of coma can result in significant increase in both survival time and survival rates (Chang *et al.*, 1978; Chirito *et al.*, 1979). This has been supported by the result of another group that treated patients in Grade III coma rather than in Grade IV coma, as shown in Table 1.12 above (Gimson *et al.*, 1978). Another group also used galactosamine rats for hemoperfusion (Niu *et al.*, 1978). Their results corroborated our findings.

Our laboratory research also shows that hemoperfusion alone increases the survival time but not the survival rates in Grade III hepatic coma rats. This may correspond to the transient recovery of consciousness in hepatic coma patients. Fresh blood exchange transfusion alone did not improve the survival time or survival rate of FHF Grade III coma rats. Two ACAC hemoperfusion combined with fresh blood exchange transfusion significantly improved the survival time of FHF Grade III coma rats, but not the survival rate. An additional hemoperfusion after the first hemoperfusion combined with blood exchange transfusion improved both the survival time and survival rate in Grade III coma rats. This seems to suggest that hemoperfusion could be one part of a more complete liver support system. This book contains chapters on more recent clinical results of its use in combination with dialysis or hemofiltration. Studies are also ongoing in using hemoperfusion to remove hepatic toxins to allow the liver to regenerate. One line of research is to combine this with the use of hepatocytes perfusion system (Rozga *et al.*, 1993; Sussman *et al.*, 1994). Another approach is to combine this with artificial cells containing hepatocytes or stem cells (Chang, 2007a, 2007b, 2007c, 2007d, 2010, 2014; Liu and Chang, 2005, 2006a, 2006b, 2009, 2012).

6. Selective Adsorbents and Immunosorbents

6.1. *Surface Modification in Immunoadsorption*

Albumin can bind tightly to the ultrathin collodion membrane of adsorbent artificial cells (Fig. 1.20) (Chang 1969a). This is initially used to increase the blood compatibility of the adsorbent artificial cells for hemoperfusion (Chang, 1969a). This albumin coating has

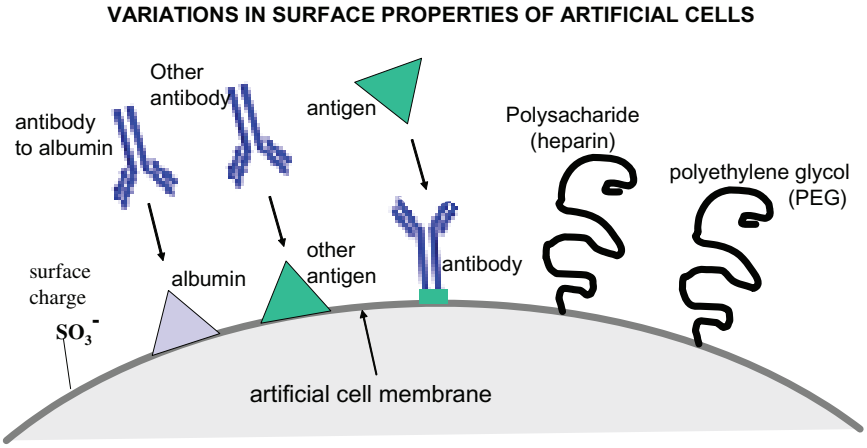


Fig. 1.20. Surface properties of artificial cell membrane can be varied by (1) incorporation of negative or positive charge; (2) incorporation of albumin to increase blood compatibility; (3) incorporation of antigens to bind antibodies or antibodies to bind antigen; (4) incorporation of polysaccharide like heparin or polyethylene glycol (PEG) to increase compatibility or retention time in circulation.

also been applied to synthetic immunosorbents resulting in blood compatible synthetic blood group immunosorbents (Chang, 1980d). In addition, Terman *et al.* (1977) show in animal studies that albumin-coated collodion-activated charcoal (ACAC) can remove antibodies to albumin. This has become a basis of one line of his research in which other types of antigens or antibodies are applied to the collodion coating of the artificial cells to form immunosorbents (Fig. 1.20). Other immunosorbents based on this principle have also been developed for the treatment of human systemic lupus erythematosus, removal of antiHLA antibodies in transplant candidates, and treatment of familial hypercholesterolemia with monoclonal antibodies to low-density lipoproteins (Terman, 1980; Terman *et al.*, 1979a, 1979b; Hakim *et al.*, 1990; Wingard *et al.*, 1991; Yang *et al.*, 2004). Antibodies have also been incorporated to the surface of lipid liposomes to allow for drug targeting to cells bearing the corresponding antigen (Torchilin, 2005). Much more recent

details are available in this book by Professor Yu's group and many other centers.

Mucopolysaccharides are important components of the surface of cell membranes. Incorporating a polyschariде, heparin, to the artificial cell membrane increases the biocompatibility and circulation time of artificial cells (Chang *et al.*, 1967, 1968). Incorporation of a synthetic polymer, polyethylene glycol (PEG), into the membrane of artificial cells, nanocapsules and lipid vesicles is even more effective for increasing biocompatibility and circulation time (Chang *et al.*, 2003; LaVan *et al.*, 2002; Torchilin, 2005). More recent extensions of this are described in detail in this book.

Albumin can bind tightly to the ultrathin collodion membrane of adsorbent artificial cells (Chang, 1969a). This was initially used to increase the blood compatibility of the adsorbent artificial cells for hemoperfusion (Chang, 1969a). In addition, albumin-coated collodion-activated charcoal (ACAC) was found to effectively remove antibodies to albumin in animal studies (Terman *et al.*, 1977). This has become the basis of one line of research in which other types of antigens or antibodies are applied to the collodion coating of the activated charcoal to form immunosorbents. Other immonosorbent based on this principle have also been developed for the treatment of human systemic lupus erythematosus, removal of antiHLA antibodies in transplant candidates, treatment of familial hypercholesterolemia with monoclonal antibodies to low-density lipoproteins and other conditions (Terman, 1980; Terman *et al.*, 1979a, 1979b; Hakim *et al.*, 1990; Wingard *et al.*, 1991; Yang *et al.*, 2004). Immunosorbents are now a very important and extensive area, and a number of chapters are devoted to them in this book.

6.2. *Synthetic Immunosorbents for Blood Group*

We have carried out a study on surface modification of synthetic immunosorbents to prevent particulate release (Table 1.13) and blood incompatibility. We used the albumin-collodion coating to synthetic immunosorbents resulting in blood compatible synthetic blood

Table 1.13. Particles Released from Uncoated and Coated Immunosorbent

Test System	Particles Released (mean + SD)
(1) Control (saline)	33 ± 7.6 (n=5)
(2) Synthetic B-immunosorbent	307 ± 12 (n=5)
(3) Albumin-Collodion coated synthetic B-immunosorbent	43 ± 8.5 (n=5)

Table 1.14. Synthetic Immunosorbent: Remove Blood Group Antibody from Plasma

	Group A	Group B
B antibodies (control)	None	Yes
B antibodies (synthetic B-immunosorbent)	None	None
B antibodies (albumin-collodion coated Synthetic B-immunosorbent)	None	None
A antibodies (control)	Yes	None
A antibodies (synthetic B-immunosorbent)	Yes	None
A antibodies (albumin-collodion coated Synthetic B-immunosorbent)	Yes	None

group immunosorbents (Chang, 1980d). The surface modified synthetic immunorsobent continues to effectively remove plasma antibody to blood groups (Table 1.14, Fig. 1.21) (Chang, 1980d). This albumin-coated synthetic adsorbent has been applied clinically for removing blood group antibodies from plasma for bone marrow transplantation (Bensinger *et al.*, 1981).

6.3. *Selective Synthetic Adsorbent for Endotoxin*

Synthetic adsorbent for the selective removal of endotoxin is also possible (Tani *et al.*, 1992). This will be discussed in detail by Professor Tani and other centers in this book.

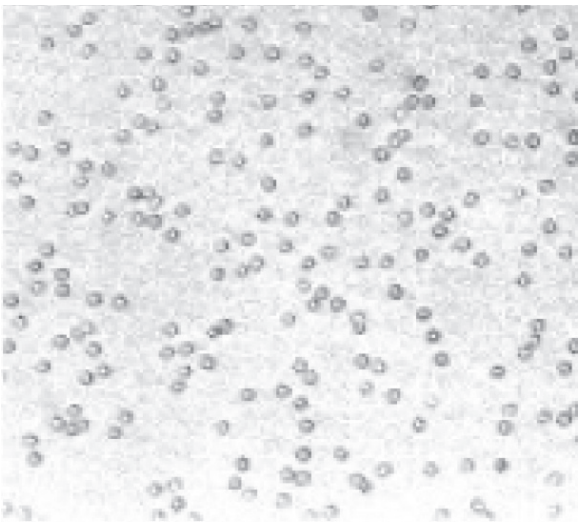


Fig. 1.21. Plasma from group A blood treated with albumin-collodion synthetic B-immunosorbent added to Group B erythrocytes. No longer caused agglutination of group B erythrocytes.

7. APPENDIX

7.1. *Detailed Procedures for the Laboratory Preparation of the ACAC Hemoperfusion Device*

(Chang, 2007a)

7.2. *Procedure for Hemoperfusion*

(Chang 2007a)

8. Useful Websites

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http://www.artificialcell.info
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