BIOCOMPATABILITY OF HEMODIALYSIS MEMBRANES

by

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ABSTRACT

With the development of biomaterials the term biocompatability was required to classify these materials in regard to their biological interaction. Biocompatability in extracorporeal blood treatments like hemodialysis is especially important, because all the pathways to bioincompatability become active , when the blood interacts with the membranes used for hemodialysis.

The objective of this thesis was to have a better knowledge about the membranes used for hemodialysis and the blood-membrane interactions.

In this study, stereomicroscopic evaluation, scanning electron microscopic (SEM) evaluation and tensile testing of the dialysis membranes have been performed. Besides these experiments, patient monitorisation and blood tests consisting of the determination of blood fibrinogen levels , complement 3 levels and white blood cell count during hemodialysis using four different membranes(Polysulfone,Cuprophan,Hemophan and Cellulose-diacetate).

Depending on the experiments performed, it can be concluded that polysulfone membranes were the best ones in terms of biocompatability, while cellulose-acetate was the worst one.

ÖZET

Yeni biomateryellerin gelişimi ile birlikte bu materyellerin biolojik ortamdaki karşılıklı etkileşimini sınıflandırmak amacıyla biyouyumluluk kavramına ihtiyaç duyulmuştur. Hemodiyalizde gibi olduğu gibi kanla ilgili ekstrakorporeal tedavi yöntemlerinde biyouyumluluk özellikle önem arz etmektedir, çünkü kan hemodiyaliz için kullanılan membranlarla karşılıklı etkileşime girdiği zaman biyouyumsuzluk mekanizmalarının tümü aktif hale gelmektedir.

Bu tezin amacı hemodiyalizde kullanılan membranlar ve kanla membranların karşılıklı etkileşimi hakkında daha fazla bilgi sahibi olmaktı.

Bu çalışmada diyaliz membranları stereomikroskop ve scanning elektron mikroskop (SEM) ile incelenmiştir ve membranlarla germe testi yapılmıştır. Bunun yanısıra dört değişik membranla (Polysulfone,Cuprophan,Hemophan and selüloz-diasetat) yapılan hemodializ esnasında hasta monitörüzasyonu, kanda kompliman 3 düzeyi, fibrinojen düzeyi tespiti ve lökosit sayımı yapılmıştır.

Deney sonuçlarına dayanılarak polysulfone membranların biokompatabilite açısından en iyi özelliklere haiz olduğu gözlenirken selüloz-diasetat membranların bu açıdan en kötü özelliklere haiz olduğu gözlenmiştir.

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

The term ***'Biomaterial'*** is generally applied to a non-viable material used in a medical device, that interacts with biological systems. The biocompatability concept was required to classify the quality of these materials in regard to their biological interaction. Almost all the biomaterials used in medicine today are derived from industrial developments for non-medical purposes. The definition of biocompatability may vary. The expression biocompatability was first mentioned in 1971,however it took a further 13 years until Klinkmann published a generally accepted definition, known as the 'no-definition'(17) . He described the requirements for biocompatability of materials in artificial organs as follows:

1. Absence of thrombogenic , toxic, allergic or inflammatory reactions,

2. No destruction of formed elements, i.e. blood cells,

3. No immunologic reactions,

4. No carcinogenic effects,

5. No deterioration of adjacent tissue...

The increase in the utilization of biomaterials in medicine during the last 15 years has caused a tremendous development in the requirements for these biomaterials to achieve the most suitable biomaterials to their intended applications. It became an obvious necessity to elucidate in addition to the blood-material interactions (haemocompatability), the material-tissue interactions and the involvement of the immune system. The knowledge of biocompatability pathways is derived from clinical observation of pathophysiology and from the results of scientific experiments. The advent of practical assay-kits for the analysis of biocompatability parameters enables biochemical laboratories to investigate even uncommon parameters. The analysis of biocompatability parameters facilitates the comparison between membranes and devices (4).

Biocompatability in extracorporeal blood treatments like hemodialysis represents a state, in which all the pathways to bioincompatability are absent or inactive. These pathways become active, when the materials of the extracorporeal system interact with the bloodstream; the products of these pathways then interact with the entire organism(2). Compared to the other extracorporeal blood processes, the need and the difficulty of eliminating sources of bioincompatability are greatest in processes used for end-stage renal disease because of the following reasons:

1. The process is employed chronically and frequently. Most of the patients have to come to the dialysis unit three days every week in order to be connected to the hemodialysis machine for four hours in every dialysis session. There are there types of hemodialysis

- Ultra short dialysis < 9 hours/week
- Short dialysis = 12 hours/week

- Long dialysis > 20 hours/week

2. In addition to materials of construction, the blood is exposed to exogenous agents contained in the dialysate(replacement fluid).

Virtually no product available for the provision of hemodialysis today can be considered biocompatible. Only the degrees of relative biocompatability can be investigated. In contrast to the 'no-definition' described above, there is a more positive description of biocompatability issued by the European Society of Biomaterials: "Biocompatability is the ability of a material to perform with an appropriate host response in a specific application" (17).

Today worldwide about 500.000 dialysis patients use more than 50 million dialysers per year. Many of these patients have been undergoing dialysis for 15 years and more. During this time the blood of each of these patients has come into contact with about 4.000 m2 of foreign surface. Worldwide average cost of one patient per year in regular hemodialysis programs is about 30.000 US dollars and that makes this therapy one of the most expensive ones among other types of medical therapies(17). In Figure 1.1, we can see the number of dialysis patients in different countries.

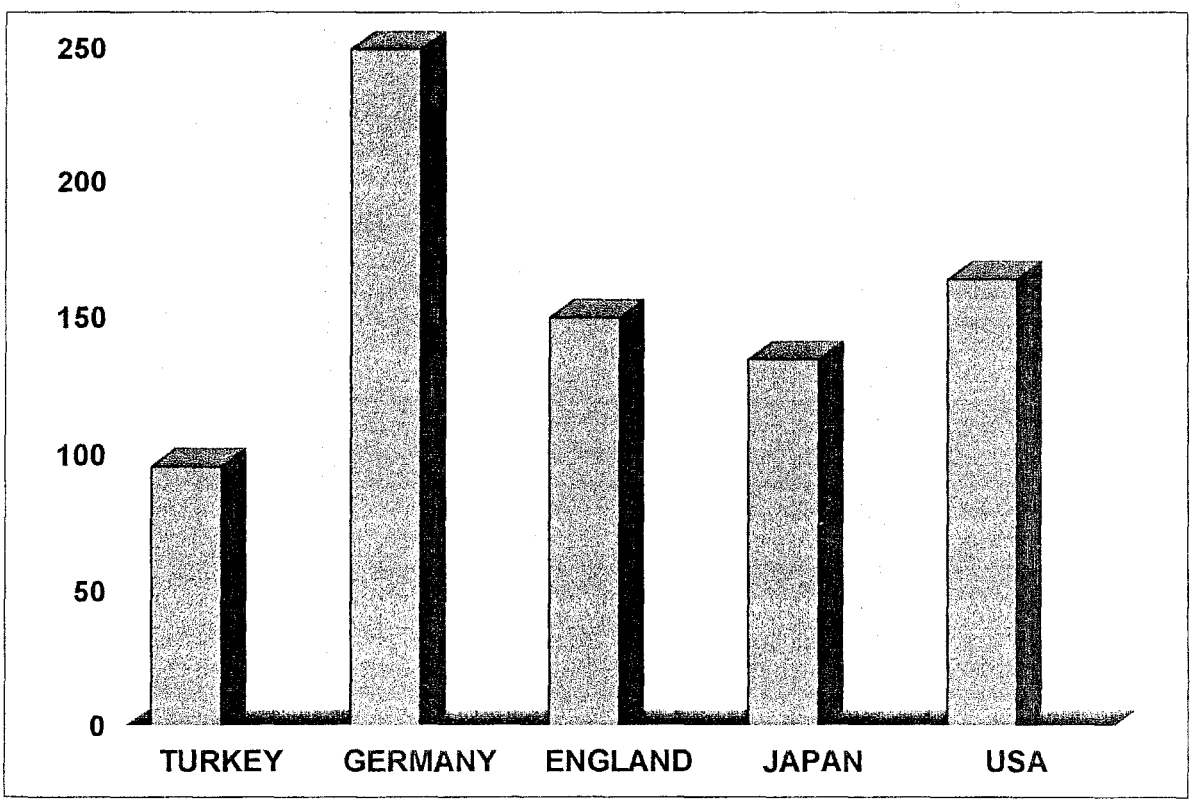

Figure 1.1: Number of dialysis patients/million population (1991 Data) (20).

Another problem is the ability to access to dialysis therapy in different countries(Figure 1.2)

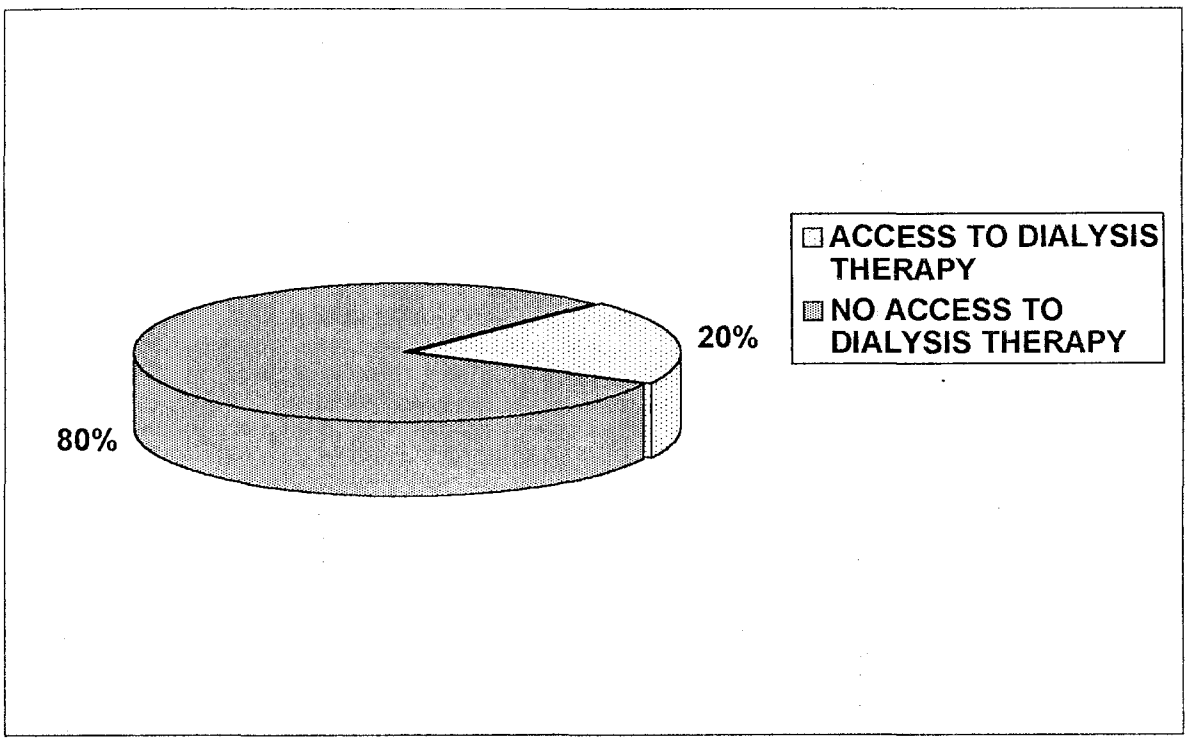

*Figure 1.2 :*Ability to access to dialysis therapy in the world (18).

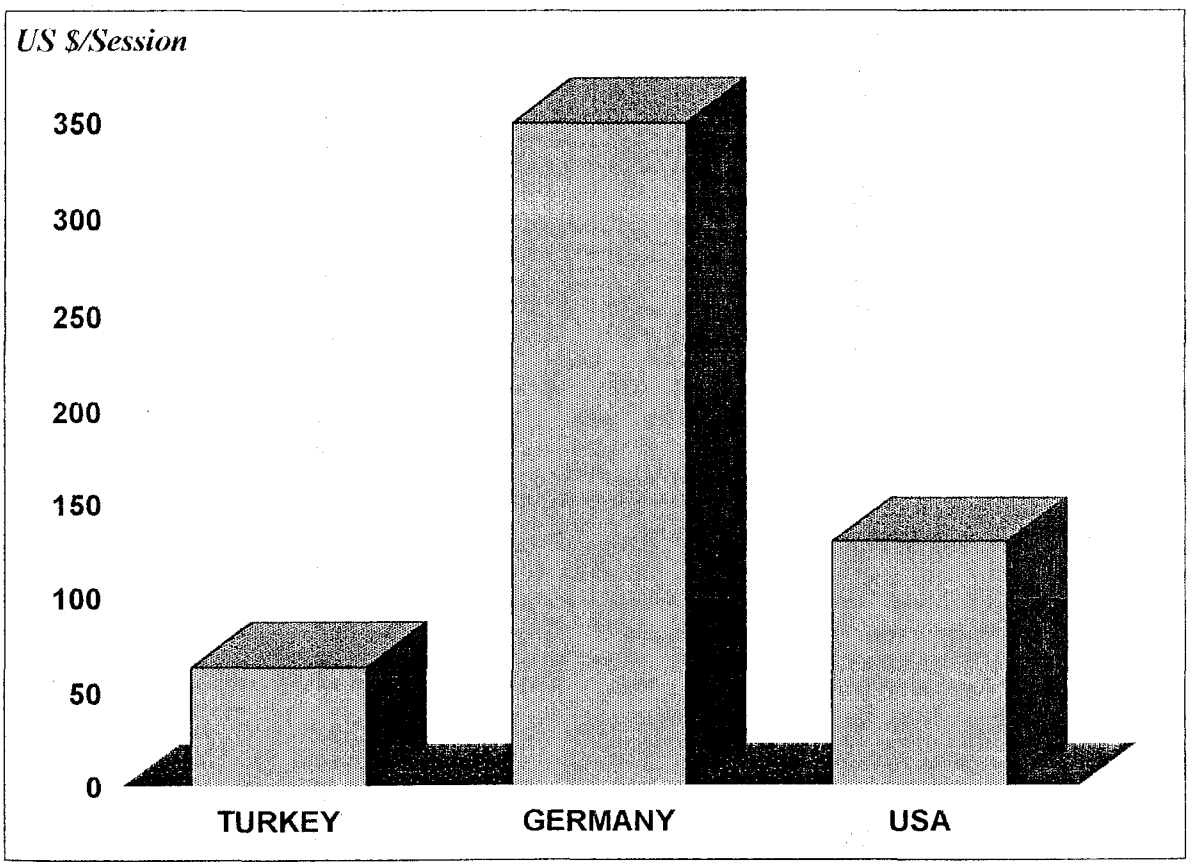

Figure 1.3 : Dialysis prices in Turkey and in other countries (20).

As seen in figure 1.3 , the amount for a dialysis session given by the government is not enough for dialysis centers to perform a high quality hemodialysis Although the dialysis sessions should be longer, it is not the case because of this reason. Figure 1.4 shows the number of dialysis sessions per week in Turkey and in other countries.

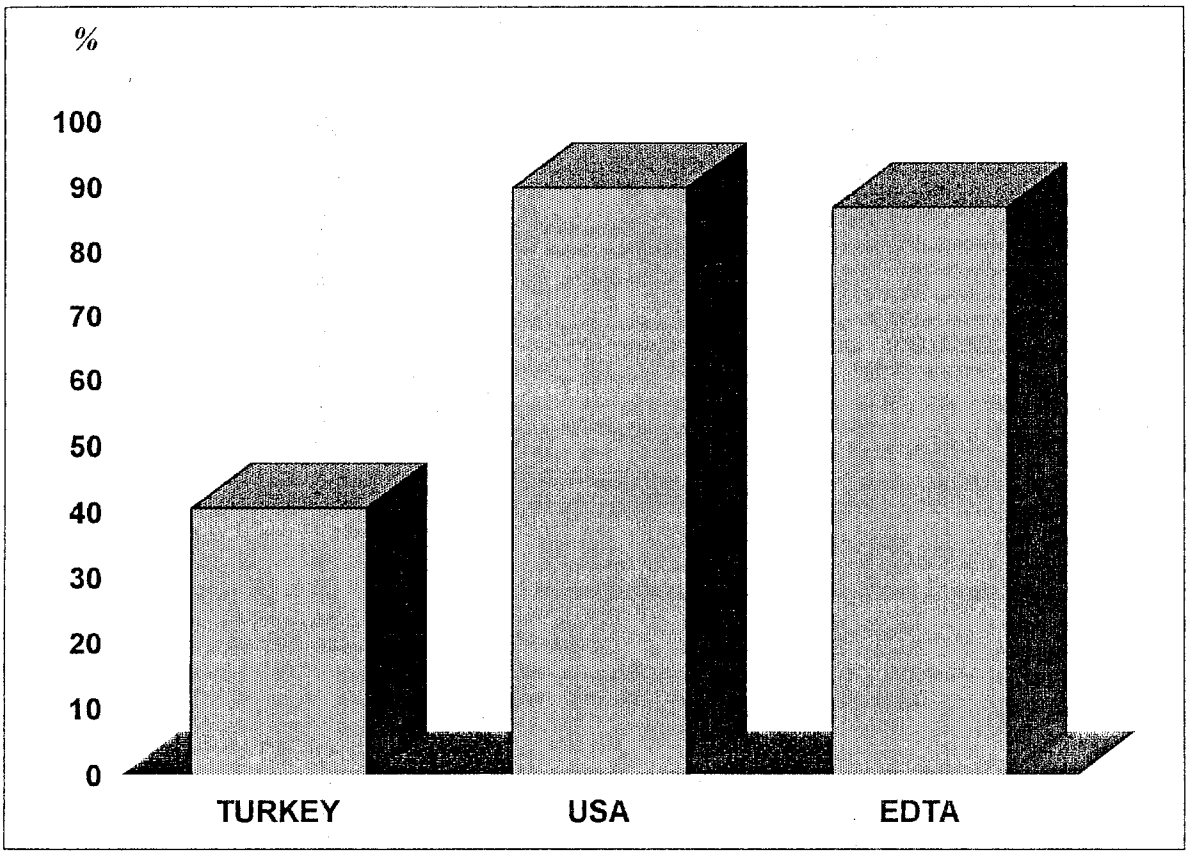

Figure 1.4 : The percentage of dialysis patients treated with three sessions of dialysis per week in Turkey , USA and in European countries (20).
EDTA : European Dialysis and Transplantation Association.

Although most of the patients should be treated three times every week , it is not the case in our countryand this situation makes a bad influence on the survival rates of these patients. Figure 1.5 shows the survival rates of ESRD patients .Another problem is the duration of a dialysis session. Due to financial reasons most of the dialysis centers in Turkey have to limit the duration of a dialysis session with maximum four hours because of financial reasons.

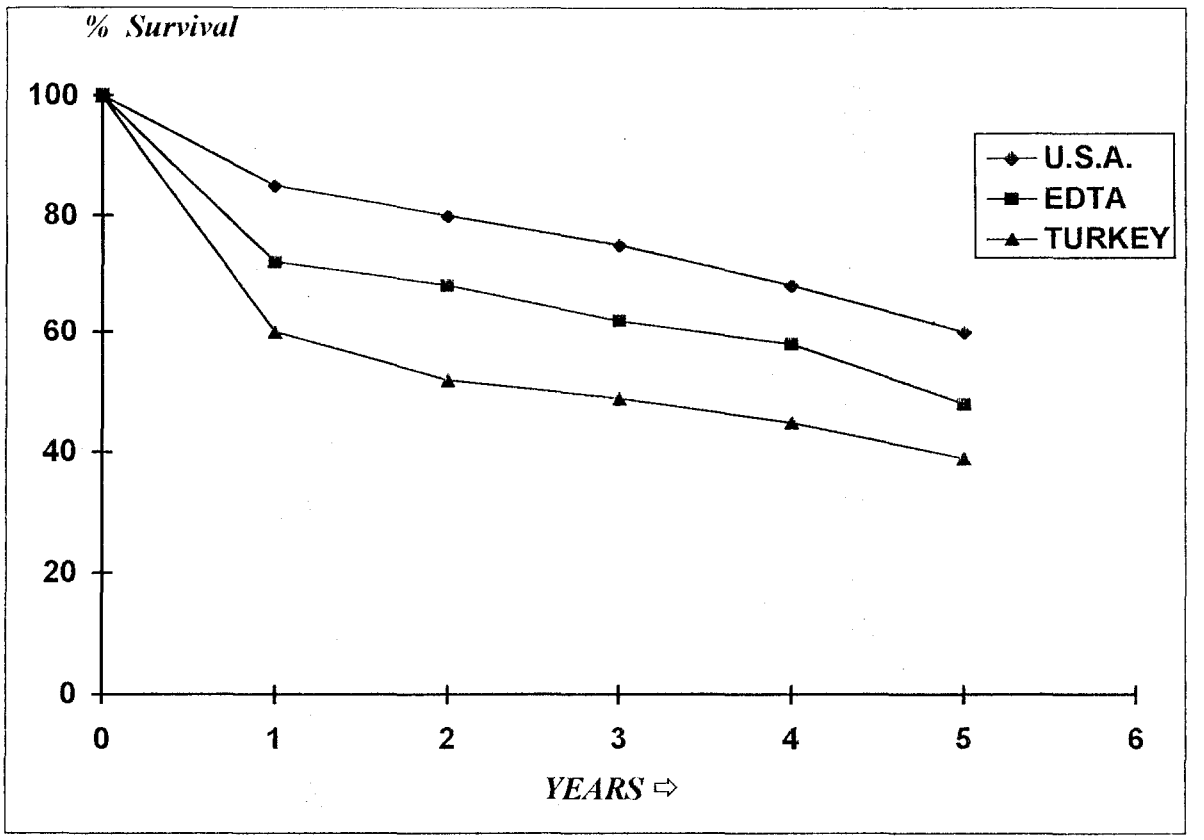

Figure 1.5. Mean survival rates of hemodialysis patients (20).

As seen in Figure 1.5 , the mean survival rate after 5 years of dialysis therapy is 60 % in the U.S.A, 48% in EDTA (European Dialysis and Transplantation Association) and 39% in Turkey (20). The reasons why the mean survival rate of dialysis patients is shorter than that in other countries are written below:

- Total dialysis time/week is not long enough.

- Less usage of bicarbonate solutions because of their high cost.

- Not using the right dialyser for the individual needs of the patient.

These data may explain the importance of dialysis therapy and the general interest in interactions of blood with extracorporeal surfaces something standardly referred as "biocompatability".

1.1. Objectives

The objective of this thesis was to have a better knowledge about the membranes used for hemodialysis and the blood-membrane interactions. Another aim was choosing a dialysis membrane material, which is the most biocompatible one among the membranes used in our experiments.

1.2. Outline of the Thesis

In the first chapter of the thesis , there is an introduction into hemodialysis and biocompatability. Historical background of hemodialysis , demopgraphical data about end stage renal failure patients and causes of end stage renal failure have been reviewed in the second chapter. Physiological transport mechanisms of the human kidney are summarized in the third chapter. In the fourth chapter , the hemodialysis procedure is explained. The experimental studies performed are shown in the fifth chapter and the conclusion of the thesis is in the sixth chapter.

2. A GENERAL OVERVIEW OF HEMODIALYSIS

In this chapter , historical background of hemodialysis, demopgraphical data about hemodialysis patients and causes of end stage renal disease have been reviewed.

2.1. Historical background

The first description of dialysis has been made by the chemist Thomas Graham from Glasgow in the year 1861.Thomas Graham would have never dreamt of that half a million patients with end-stage renal failure would owe their lives to this therapy today. After Graham's description of dialysis 52 years have passed until it became experimentally possible to perform dialysis on dogs by Abel and Coworkers in 1913.Abel used membranes made of collodium , a cellulose nitrate , but its small surface area and thick blood columns were incompatible with rapid mass transfer .In 1920 , Lore tried to use intestinal membranes as dialysis membranes.After this attempt Heyde and Haas tried to perform dialysis with membranes made of fishbladder and parchment(16,18).

The idea of performing dialysis with the help of natural membranes has led Ganter to realize the first peritoneal dialysis in the year 1923. In 1938 , Thalheimer also demonstrated inadequate mass transfer with a small device , using cellophane tubing as membranes(18).

Dr.Willem Kolf developed a machine with large surface area ,thin blood columns, and adequate blood mixing in 1943.His artificial kidney used a 30 foot long, hollow cellophane tube wrapped around a 2 foot diameter drum. Propulsion of the blood through the tube was by means of Archimedes principle. The tube lay in a bath of approximately 50 liters that was changed at least once during the dialysis. More than 2 m2 surface area was available in this artificial kidney. Clearance of urea from blood was nearly equal to blood flow rate . Kolf's initial experiments established roughly the treatment schedule , dialysate composition , and clearance rates necessary for the uremic patient . In 1947 , Alwall performed the first dialysis with ultrafiltration(18).

The artificial kidney was used extensively in the treatment of acute renal failure during the 1950's. In 1955 the first coil dialyser , the first major type of the dialysers , has been developed . The main goal of developing dialyser membranes was a smaller and a more convenient hemodialyser with large surface area , low blood flow resistance , and high clearance. Within the following years two other major types ,the parallel plate dialyser and the hollow fiber dialyser , have been developed. Meanwhile , the research to find the best membrane material was still going on .

It was not possible to perform successful long term dialysis treatment until the 1960's. In the last two decade many types of cellulose based and synthetic dialysis membranes were

available in the market. Since the 1970's , emphasis has been placed on relative comparisons of both host and the biomaterial and biomechanical properties(7). Not only the membranes also the dialysis machines have shown great improvement compared to their ancestors. Microprocessor controlled dialysis machines,that allow the patients to feel much better during the dialysis session, came widely into clinical practice in the last five years .

2.2. DEMOGRAPHICAL DATA

Before the early 1960's , patients who developed end-stage renal failure faced an inevitable death within days to weeks.The introduction of hemodialysis, peritoneal dialysis and renal transplantation has enabled these patients to survive for many years, which resulted in a large population of patients on dialysis therapy(1).

According to US Renal Data System (USRDS), the number of patients with End-stage Renal Disease (ESRD) and receiving dialysis therapy was 163.000 or 654/million in 1989. As seen in Figure 2.2.1 the number of these patients is increasing dramatically. USRDS data show, hat the 1978 incidence was 68/million as compared 166/million in 1989.The growth rate of incidence is 10.4%/year and the growth rate of the prevalence is 8.4%/year(1).

At the end of 1989 , 54.5% of the ERSD patients were male and the rest were female according to USRDS data(1). The distribution of these patients with respect to the sex is same . Of the total ESRD population in the US, 66% are white,29% are black. As the blacks constitute about only 12% of the total US census population, this proportion suggests the existence of much higher risk for the black population.

In other countries, the incidence of patients initializing ESRD therapy has continued to rise. (Fig. 2.2.2)

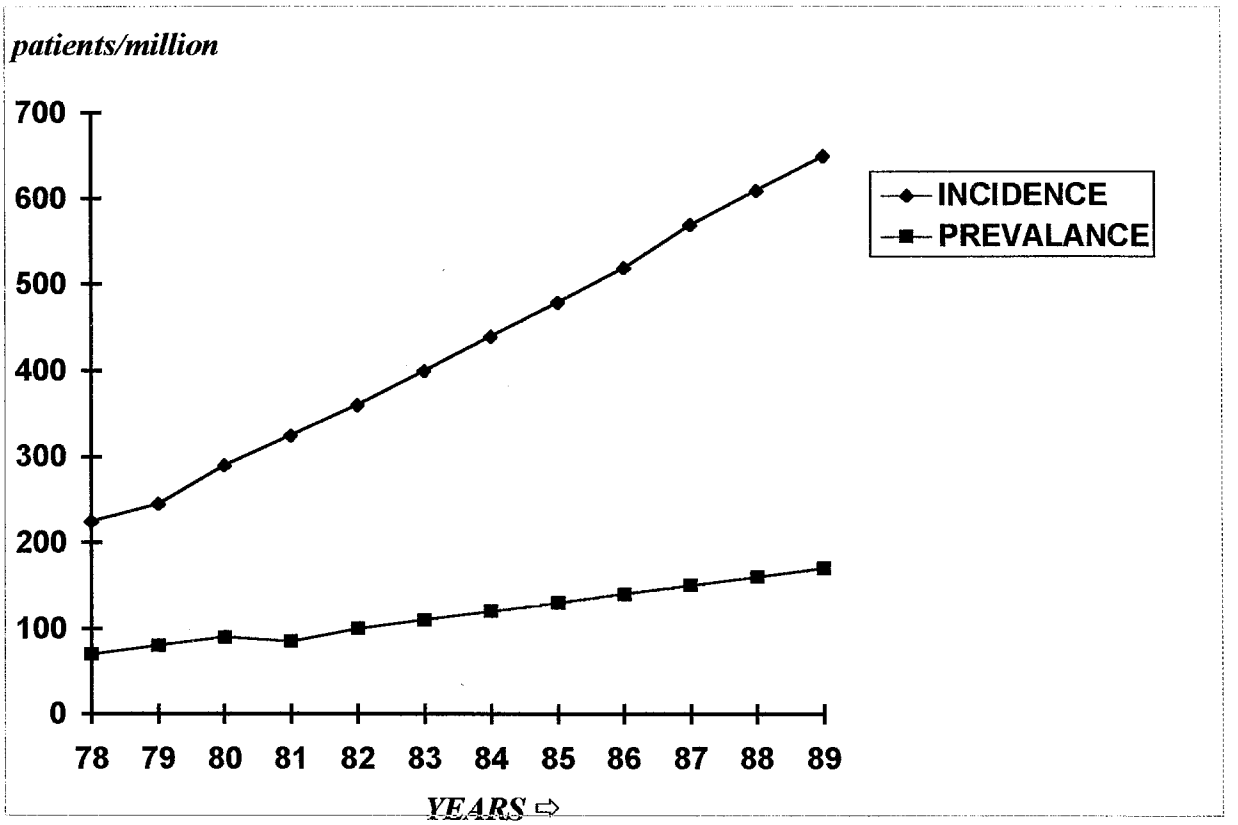

Figure 2.2.1 :The incidence and prevalence of ESRD patients between the years 1978 and 1989 (1).

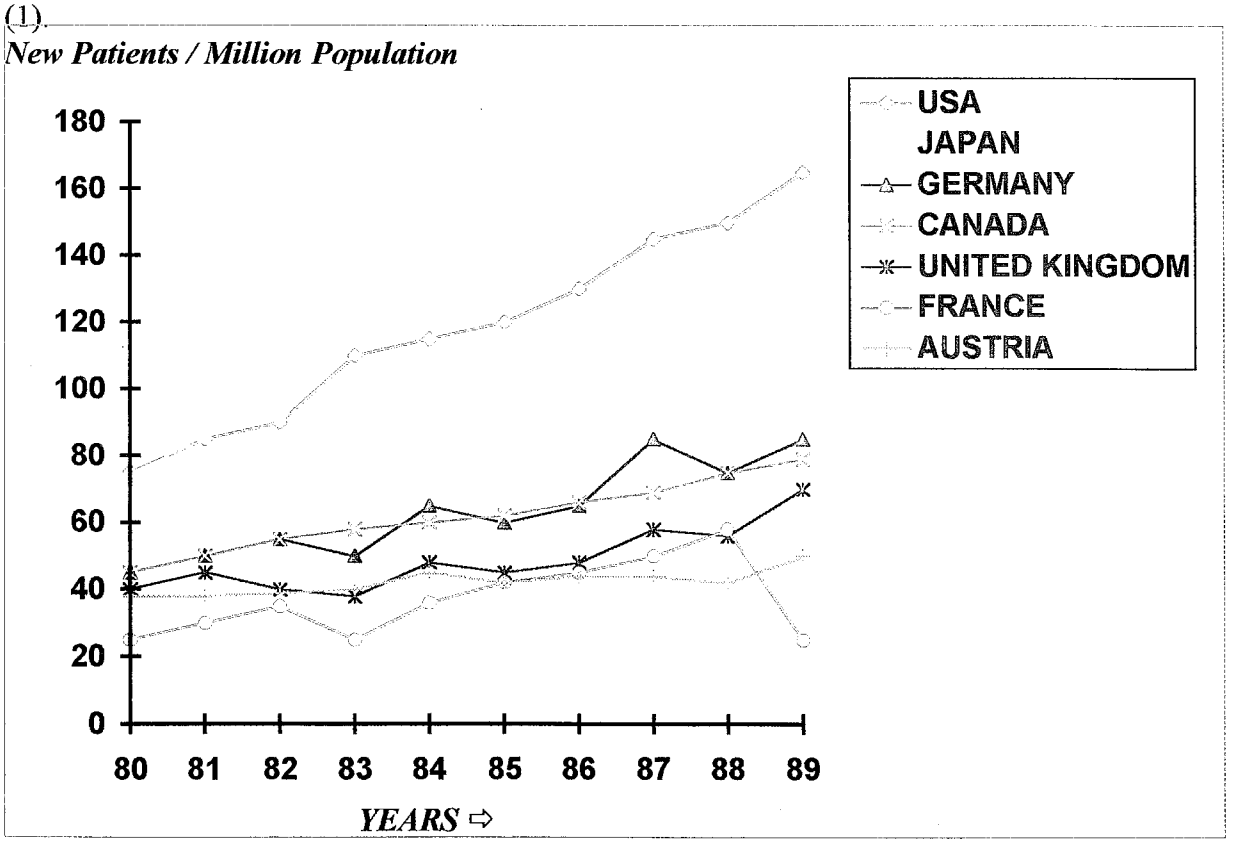

Figure 2.2.2:The incidence of patients initializing ESRD therapy in different countries(1).

All registries lack information on patients dying of chronic uremia, who have not undergone renal replacement therapy.The number of patients dying within 90 days of treatment or dying with chronic uremia without dialysis is unknown and are not included in these data.

To estimate the true incidence and prevalence of patients treated with dialysis therapy , an additional increase of 7.5% is required, resulting in an incidence of 178/million and a prevalence of 703/million in the United States.On the other hand, it can be seen that treated ESRD prevalence has increased from 220 to 654 patients/million between 1978 and 1989 (1).

Figure 2.2.3 shows the age distribution of ESRD patients at the end of 1989.Of the total ESRD population , the age group the peak percentage of the patients is the sixth decade.The median age of new patients has increased from 55 years in 1980 to 61 years in 1989.The smallest percentages occur at the extremes of age, in the very old and very young.

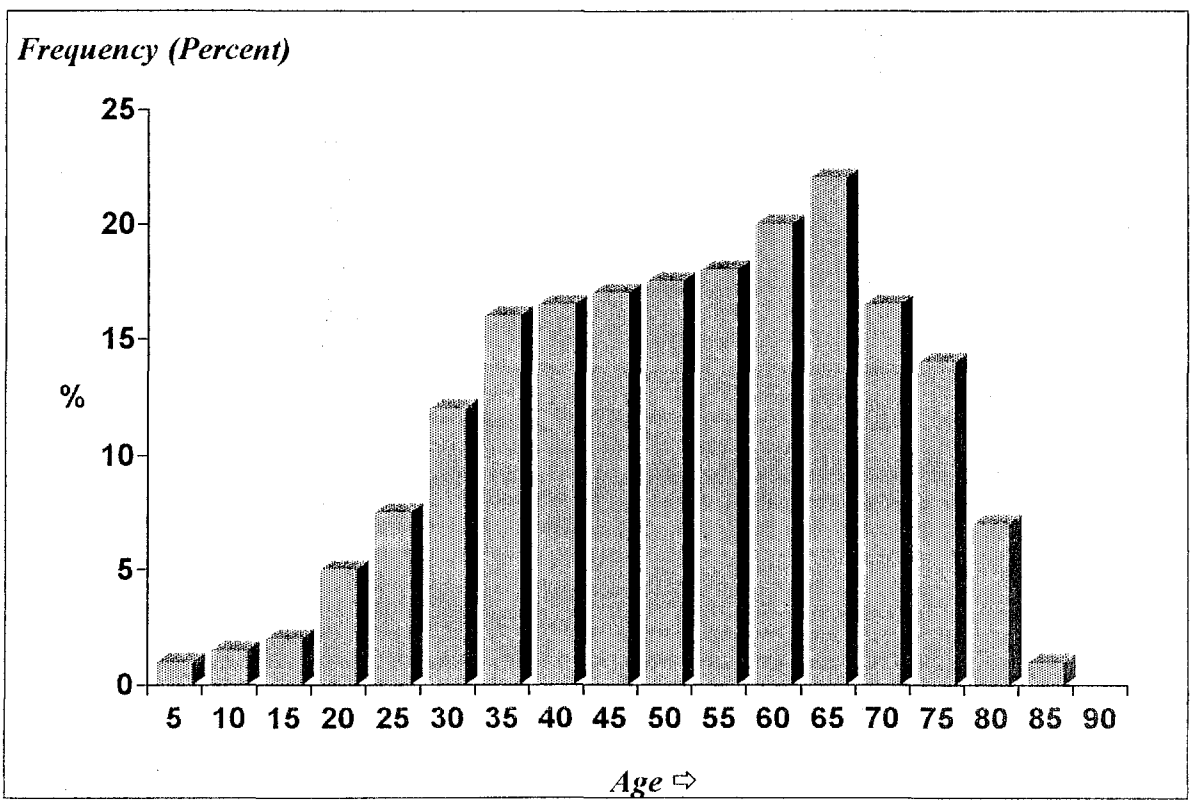

Figure 2.2.3: Age distribution of ESRD patients at the end of the year 1989 (1) .

In 1989 the most common treatment modality for ESRD in the US was center hemodialysis (57%) , followed by a functioning transplant (25%) , peritoneal dialysis (9%) , home dialysis (2%) and unknown (7%).Over the last decade, the number of functioning transplants are increasing.The small percentage of patients on home dialysis has been decreasing over the last years.Utilization of various treatment modalities for ESRD varies considerably by country.For example , peritoneal dialysis is preferred mostly in the UK (43.9%) ,Canada (31.7%) and Australia (31.1%).Home dialysis is more frequently used in Australia (21.3%).The most common form of ESRD therapy in the Netherlands is renal transplantation.50% of their ESRD population has a functioning graft (1).

2.3. CAUSES OF END-STAGE RENAL DISEASE (ESRD)

ESRD has many causes, including primary renal diseases, systemic diseases involving the kidney, and inherited diseases.The various etiologies can be classified into six main groups:

1. ***Diabetes***
2. ***Hypertension***
3. ***Glomerulonephritis***
4. ***Cystic disease***
5. ***Urological abnormalities***
6. ***Other***

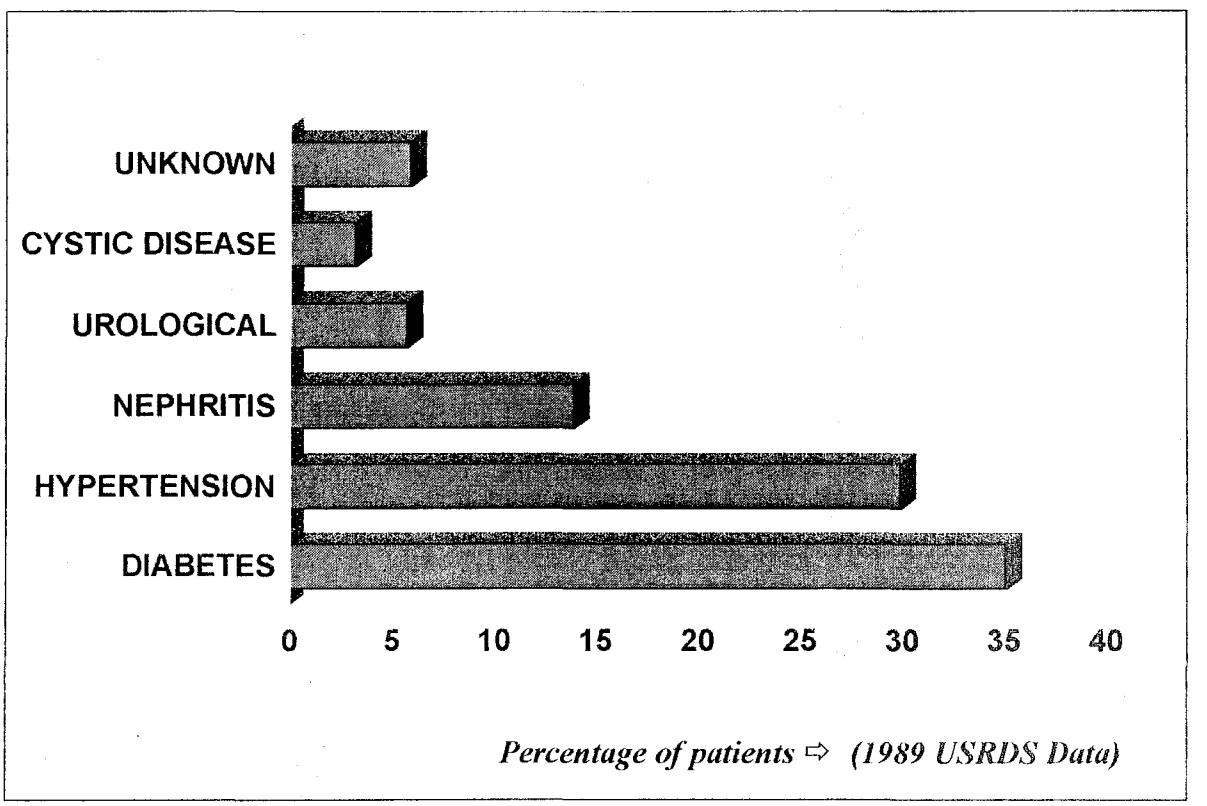

Figure 2.3.1: Causes of end-stage renal disease (1) .

As seen in Figure 2.3.1, diabetes and hypertension are two main causes of ESRD and the number of new ESRD patients due to two etiologies mentioned is increasing more dramatically than that of other causes.

3. *OVERVIEW OF RENAL FUNCTION*

The constancy of the bodies internal environment is maintained by the continuos functioning of two kidneys, which consist of nephrons(Figures 3.1 and 3.2). A nephron consists of a renal tubule and a glomerulus. As blood passes through the kidneys, the nephrons clear the plasma of unwanted substances (e.g. urea), while retaining other essential substances. Unwanted substances are removed by glomerular filtration and renal tubular secretion and are passed into the urine. Substances, that the body needs, are retained by renal tubular absorption and are returned to the blood by reabsorbtive processes (6).

In the ***glomerular filtration*** process, a fluid like plasma is filtered through the glomerular capillaries into the renal tubules. As glomerular filtrate passes down the tubules, its volume is reduced and its composition altered by the processes of ***tubular reabsorption*** (removal of water and solutes from the tubular fluid) and ***tubular secretion*** (secretion of solutes into the tubular fluid) to form urine. A comparison of composition of the plasma and an average urine specimen illustrates the magnitude of some of these changes and emphasizes the manner, in which wastes are eliminated, while water and important electrolytes and metabolites are conserved(Table 3.1) .

Table 3.1: Urinary and plasma concentrations of some physiologically important substances (6).

Substance	*Concentration in* *Urine (U)*	*Plasma (P)*	*U/P Ratio*
Glucose (mg/dl)	0	100	0
Sodium (mEq/L)	150	150	1
Urea (mg/dl)	900	15	60
Creatinine (mg/dl)	150	1	150

Furthermore, the composition of urine can be varied and many homeostatic regulatory mechanisms minimize or prevent changes in the composition of the extracellular fluid (ECF) by changing the amount of water and various specific solutes in the urine . The kidneys are also endocrine organs (hormone secreting) ,secreting renin and the renal erythropoietic factor.

3.1. Types of Transport Mechanisms in the Kidney

There are two main types transport mechanisms in the human kidney . These are the capillary membrane transport and renal epithelial transport mechanisms.

3.1.1. Capillary Membrane Transport Mechanisms

Convection: is the bulk transport of a fluid with its dissolved small solutes across a membrane, which is caused by a hydrostatic pressure difference between the glomerular capillaries and the Bowman's capsule. The filtered load of the solutes is proportional to the glomerular filtration rate and to the forces, that affect filtration, namely the hydrostatic and oncotic pressures (6).
Simple diffusion: is the movement of solutes from areas of higher concentration to areas of lower concentration.

3.1.2. Renal Epithelial Transport Mechanisms

There are basolateral membrane transport systems and apical membrane transport systems (Figure 3.3). Basolateral membrane transport systems are the following:

-***Primary active transport mechanism*** of the Na-K-ATPase pump system transports sodium ions against an electrochemical potential from the cell interior and maintains a low intracellular sodium concentration (6).

-***Facilitated diffusion*** translocates glucose from the intracellular fluid across the membrane to the interstitial fluid. Facilitated diffusion involves the passive transport of a substance by a protein carrier from a region of higher concentration to a region of lower concentration (6).

Apical membrane transport systems consist of the following mechanisms:

-***A diffusion mechanism*** is available for sodium ions to pass through the tight junction .

-***Carrier mediated mechanism*** is responsible for active (uphill) transport of other solutes, such as glucose,amino acids. The transport of sodium down its gradient provides energy for this active transport (6). There are two types of Na-dependent transport systems:

1. Cotransport denotes the transport of two substances by a protein carrier in the same direction .
2. Countertransport defines the transport of two substances by a protein carrier in the opposite directions.

-***Osmosis*** is the process of net diffusion of water from a region of higher activity (or lower solute concentration) to a region of lower water activity (or higher solute concentrations)

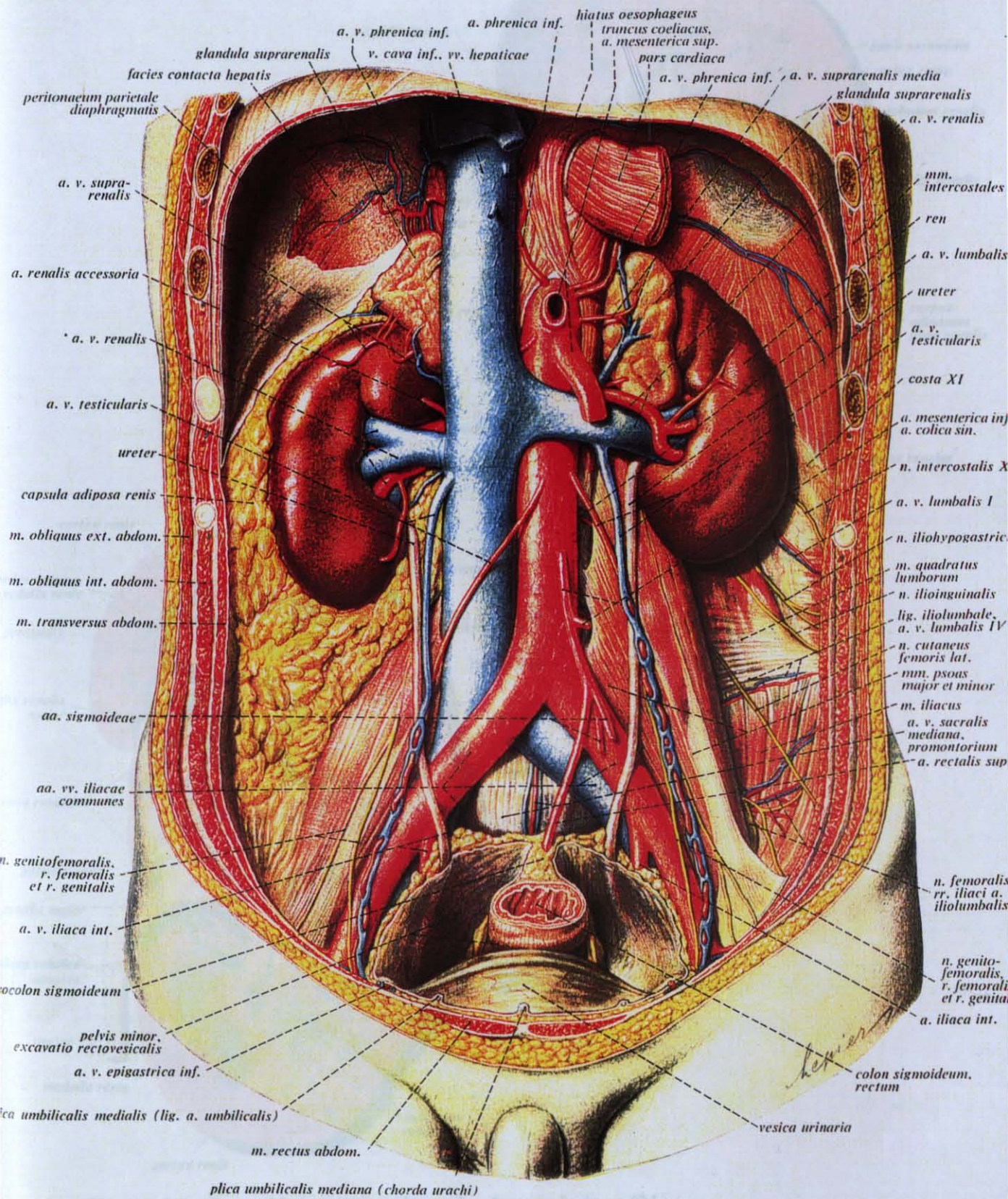

Figure 3.1 : Abdominal organs in the dorsal body wall (21).

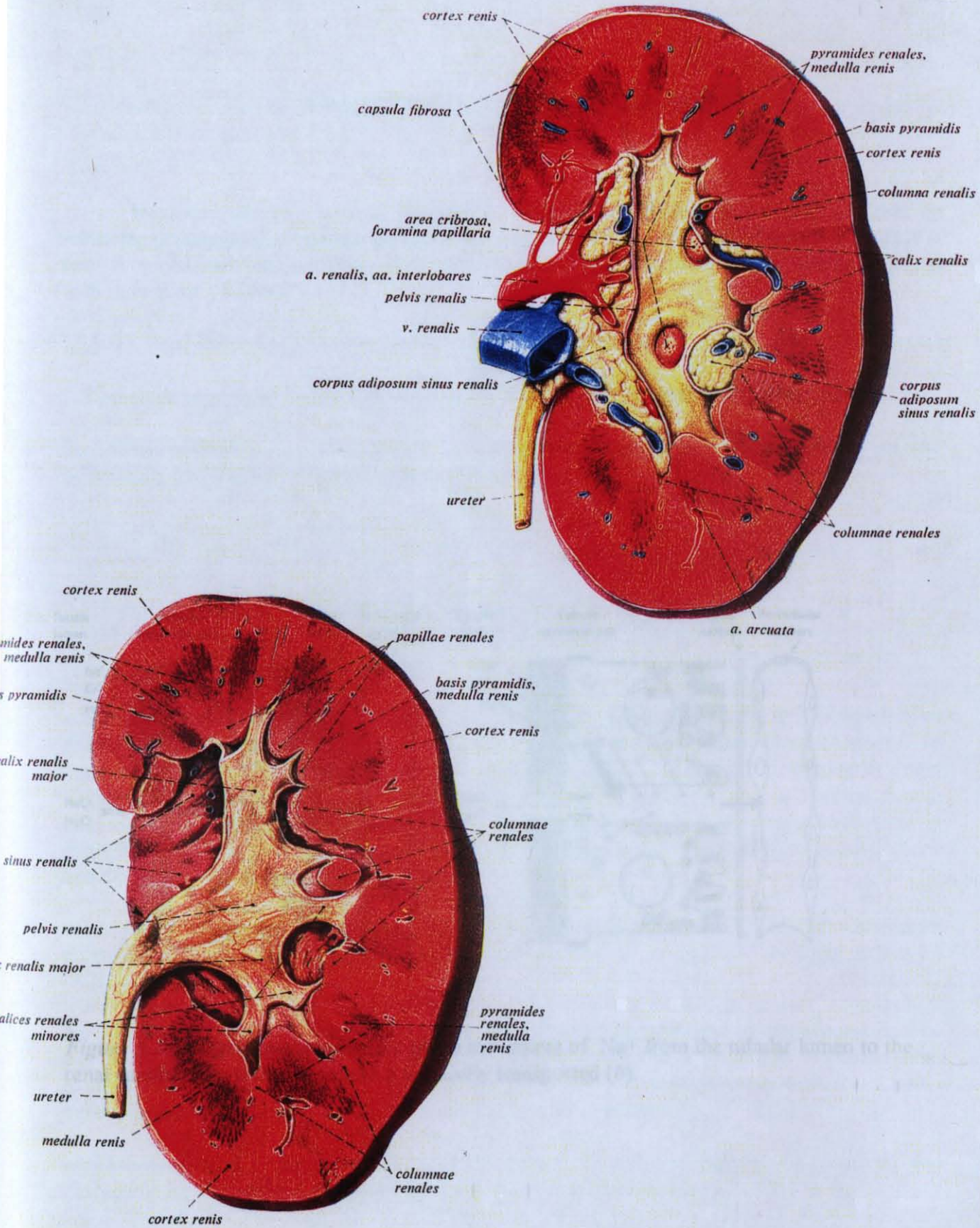

Figure 3.2. Frontal hemisection through a human kidney (21).

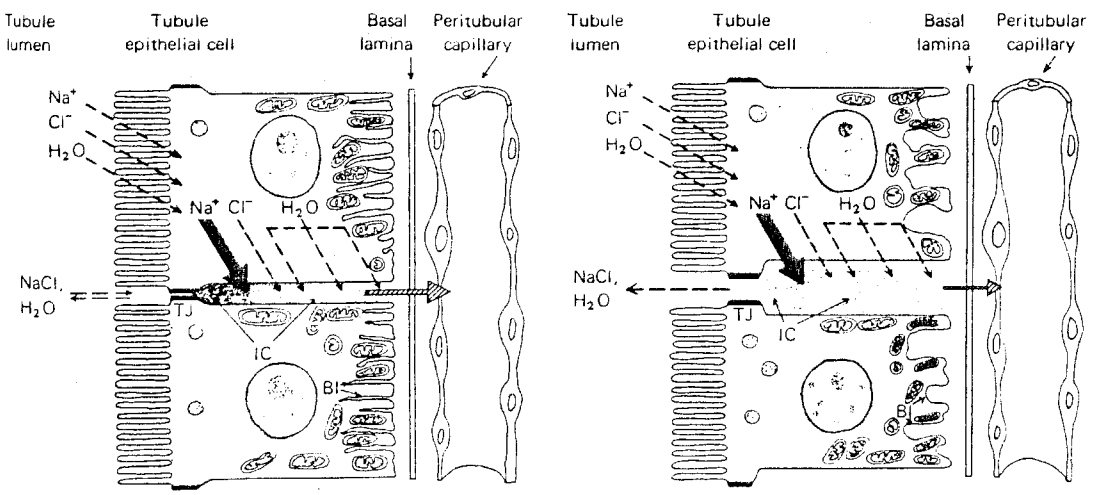

Figure 3.3 : Diagrammatic summary of the movement of Na+ from the tubular lumen to the renal capillaries in locations where it is actively transported (6).

4. THE HEMODIALYSIS PROCEDURE

Hemodialysis is a treatment designed to correct the chemical composition of blood by removing accumulated metabolic products and adding buffer in a process of diffusion through a natural or synthetic semipermeable membrane (1).This kind of treatment is required for patients with three main problems :

1. Acute renal failure (presumed reversible until proved otherwise)

2. End-stage renal failure (presumed irreversible until treated by renal transplantation)

3. Severe poisoning (in some forms of severe poisoning extracorporeal removal of the poison may be beneficial or actually life-saving)

4.1. Definition of Terms Used in Hemodialysis:

acute allergic reaction : a hypersensitivity reaction based on type I hypersensitivity,which is an anaphylactic reaction involving IgE antibodies without the activation of complement. In hemodialysis type I hypersensitivity is based on ethylene-oxide-induced IgE activation or direct complement activation.The clinical signs include a warm sensation, pruritus, and lacrimation in mild reactions; bronchospasm, angiooedema, uriticaria, nausea, vomiting and back pain in moderate reactions; and intense abdominal pain , cardiovascular collapse, hypotension, shock and death in severe systemic reactions(1) .

acute phase response : the primary response to infection or injury from cellular activation producing systemic effects such as fever and the production of 'acute phase' proteins such as C-reactive protein(1).

anticoagulation : method to prevent coagulation of blood by inhibition of coagulation factors, e.g. factor Xa and IIa(thrombin).This method is commonly used in hemodialysis as used in other extracorporeal circulations such as heart-lung machine.For this purpose heparin or low-molecular-weight heparin is added to the extracorporeal circulation(1).

antithrombogenic : An antithrombogenic surface is one, in which the material has characteristics that prevent coagulation , e.g. heparin coated surfaces (1).

clot formation : the formation of a solid or semi-solid mass from the transformation of fibrinogen to cross-linked fibrin by the action thrombin, the result of the coagulation cascade and containing cells trapped in a fibrin mesh(1).

complement activation : the activation of the complement cascade either by the classical or alternate pathway. In extracorporeal circuits it is an activation as a result of blood-material or blood-device interaction or by heparine-protamine interaction(1).

dialysis fluid (dialysate) : an electrolyte solution used in dialysis to provide a concentration gradient across the membrane for transport of certain solutes to maintain the physiological concentration of other solutes such as sodium,potassium,magnesium and calcium.For this purpose two different buffer solutions, acetate or bicarbonate solutions , are used(1).

dialyser : a device, which permits diffusion or convection to move substances from one compartment to another across a semi-permeable membrane(1).

endotoxin : lipopolysacccharides with varying molecular weights and structures derived from the outer membrane of Gram-negative bacteria, capable of inducing inflammatory reactions including activation of cells, complement and coagulation(1).

first-use syndrome : a hypersensitive reaction observed in patients treated with a new (unused) dialyser .The clinical manifestations are varied. Symptoms usually occur during the first 10 minutes of dialysis , but may be delayed up to 2 hours(1).

heparin : one of the major anticoagulant drugs used in medicine, which prevents fibrinogen to form a fibrin clot.There are two types of heparin , a standard (unfractionated) heparin and a low-molecular-weight (fractionated) heparin(1).

high flux dialysis . hemodialysis using a dialyser with a high flux membrane, a dialyser membrane characterized by high hydraulic permeability. (1)

IgE (Immunglobulin E) : are antibodies secreted by plasma cells . IgE Antibodies release histamin from basophils and mast cells(6).

non-thrombogenic : the properties and characteristics of a material (or device) that leads to minimal or no thrombus formation(1).

platelet : a blood cell without a nucleus and having a number of functions related to haemostasis(1).

transplant . an organ or tissue taken from the body for grafting into another area of the same body or into another individual. (1)

During hemodialysis or the interdialytic period following complications can be seen:
-Hypertension and cardiovascular disease ,
-Anemia,

-Peripheral neuropathy,
-Bone disease and calcium problems,
-Hepatitis and AIDS,
-Bleeding disorders,
-Muscle cramps,
-Electrolyte imbalance,
-Impairment in the metabolism of amino acids,
-Itching
-Nausea and vomiting
-Depression and other psychological problems.

The fundamental assumption of dialysis treatment is that some ureamic abnormalities or a function of concentration of ingested or metabolically produced toxic materials which are normally excreted by the natural kidney. In the patient with the declining renal function , concentration of these solutes rises and at some point, the removal of these solutes must be supplemented by exogenous means like hemodialysis therapy. Currently this is achieved through a wide variety of dialysers , which have considerable variability in their transport properties.

Pharmacokinetic models can be applied to intermittent dialysis therapy. This concept is better appreciated, if dialysis is viewed in terms of negative drug administration.; that is, instead of administering some chemical substance over spaced intervals , toxic materials are being removed over a similar interval. The magnitude of this therapy can be viewed as the amount of frequency of this removal. In the dialysis therapy a large number of materials are being removed , all of them at unequal rates. It is with regard to the measurement and control of such substances, that the concept of mass balance and solute kinetics can provide powerful tools and insights for the evaluation and guidance of this treatment.

Hemodialysis generally performed in hospitals with Nephrology departments.For performing hemodialysis we need the following:

1.A water treatment system

2.Vascular access to the patient

3.Hemodialysis machine

4.Dialyser

5.Blood tubing for circulation

6.Dialysate solutions

7.Anticoagulation

8.Medical staff specialized in hemodialysis

4.2. Water Treatment for Dialysis

A water treatment system provides water, in which levels of contaminants known to be toxic to dialysis patients are consistently below regulated limits (Table 4.2) .The system provides water at the correct temperature, pressure and flow rate for the operation facility of the equipment. All dialysis facilities require a water treatment system , because no water supply can be relied on to provide to provide water, which meets the concentrations as described in Table 4.2 .

Table .4.2: Maximum concentrations of contaminants permitted in water used for the preparation of the dialysate (1).

Contaminant	Maximum Concentration (mg/L)
Substance normally included in the dialysate	
Calcium	2.0
Magnesium	4.0
Potassium	8.0
Sodium	70.0
Toxic substances	
Arsenic	0.005
Barium	0.1
Cadmium	0.001
Chromium	0.014
Lead	0.005
Mercury	0.0002
Selenium	0.09
Silver	0.005
Other substances identified as toxic in hemodialysis	
Aluminum	0.01
Chloramines	0.10
Free chlorine	0.5
Copper	0.10
Fluoride	0.20
Nitrate (as N)	2.0
Sulfate	100.0
Zinc	0.10
Microbiologic contaminants	
Bacteria	200 CFU/ml

The water system should be able to cope with the peak demand of the dialysis facility.

The water treatment system consists of a depth filter, a carbon filter, a softener, a 5 micron filter, a reverse osmosis system, a water storage tank and a UV light source(Figure 4.2). The carbon filter is used for removing chloramines from water.Calcium and magnesium can be removed by reverse osmosis, but shortens its life . Therefore, a softener to remove calcium and magnesium is installed in the system. The primary water purification process in most applications is the reverse osmosis unit.While ion exchange produces higher quality water with regard to ionic contaminants, it increases microbiologic contamination and has higher costs than reverse osmosis does. Reverse osmosis effectively reduces the level of inorganic contaminants in the water by a factor of 10. Such a reduction is sufficient to produce the required water standards.

Other pretreatment may include a depth filter to remove suspended solids and a 5 micron particle filter to remove the particles, that may damage the reverse osmosis system.All filters must have opaque housing to inhibit algae growth.The UV light source is used for minimizing the bacterial population in the dialysate(1).

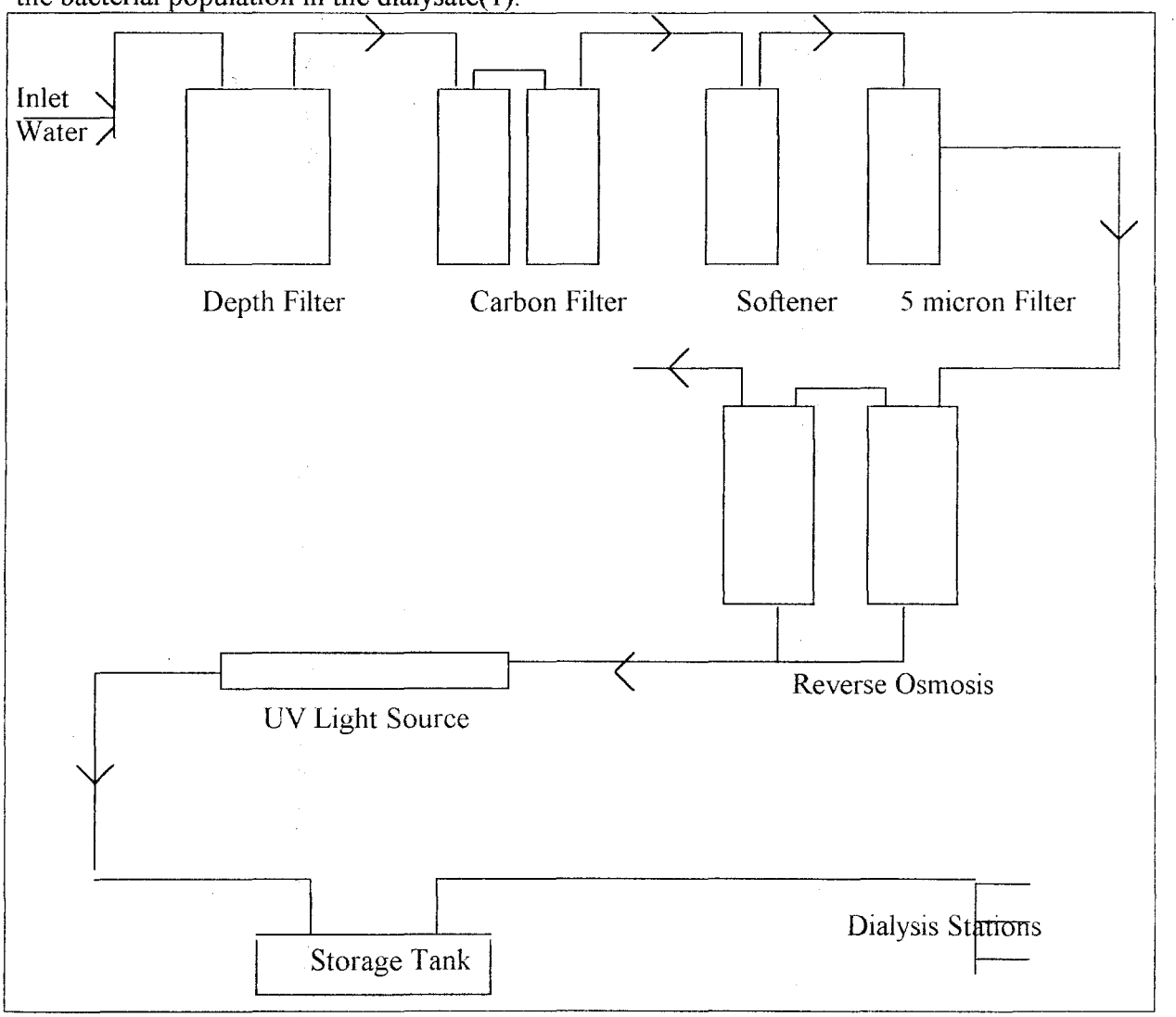

Figure 4.2: The schematic diagram of the water treatment system (1).

4.3. Vascular Access

The way of vascular access depends on the patient, who needs hemodialysis. For example vascular access for patients, who have to be treated with hemodialysis because of severe poisoning or acute renal failure a double lumen,semi stiff, tapered ***femoral*** or ***subclavian catheter*** is introduced into the femoral or subclavian vein of these patients.But this procedure requires skill and experience for their insertion. But on the other hand, providing safe and reliable access to the blood for hemodialysis remains a cause of difficulty even today.There are two types of surgical procedures for this purpose (Figure 4.3) (1):

- ***Direct arterivenous fistulas*** :

This method is the most preferred of vascular access for chronic hemodialysis. This procedure consists of a side-to-side radial artery cephalic vein anastomosis of 0.5 or 1cm .The failure rate of this method is between 20 and 30%.

- ***Graft arteriovenous fistulas*** :

The forearm is the most commonly preferred site for graft placement.The arterial inflow of the graft is provided by radial,ulnar or brachial artery and venous outflow into a large antecubital vein or upper arm basilic vein. After this method , reoperation is inevitable and the two-year patency rates are 70-80%, with average duration of patency of 1.7 to 4.8 years.

4.4. The Hemodialysis Machine

Technological advances in hemodialysis machines offer nephrologists tremendous flexibility in adjusting dialysis regimens to address individual patient needs (Figure 4.4.1).

The central component of the dialysate delivery system is the proportioning unit that can reliably provide proportioning of water and the dialysate concentrate. It has to deliver continuously dialysate of highly controlled concentration and temperature (1,3,6). The flow rate of the dialysate and pressure can be controlled over a specified range. There are safety monitoring systems for internal monitoring of concentration and temperature and this system is activated to bypass the dialyser if concentration and/or temperature fall outside the specified limits. The system uses a conductivity monitor of the dialysate to adjust to adjust the proportioning of the dialysate. Some machines provide dialysate pH monitoring as an additional safeguard to avoid mixing of an improper concentrate(Figure 4.4.2)

Blood and dialysate pumps control flow through their respective chambers in the dialysis circuit. After the blood pump has been stabilized the venous and arterial limit

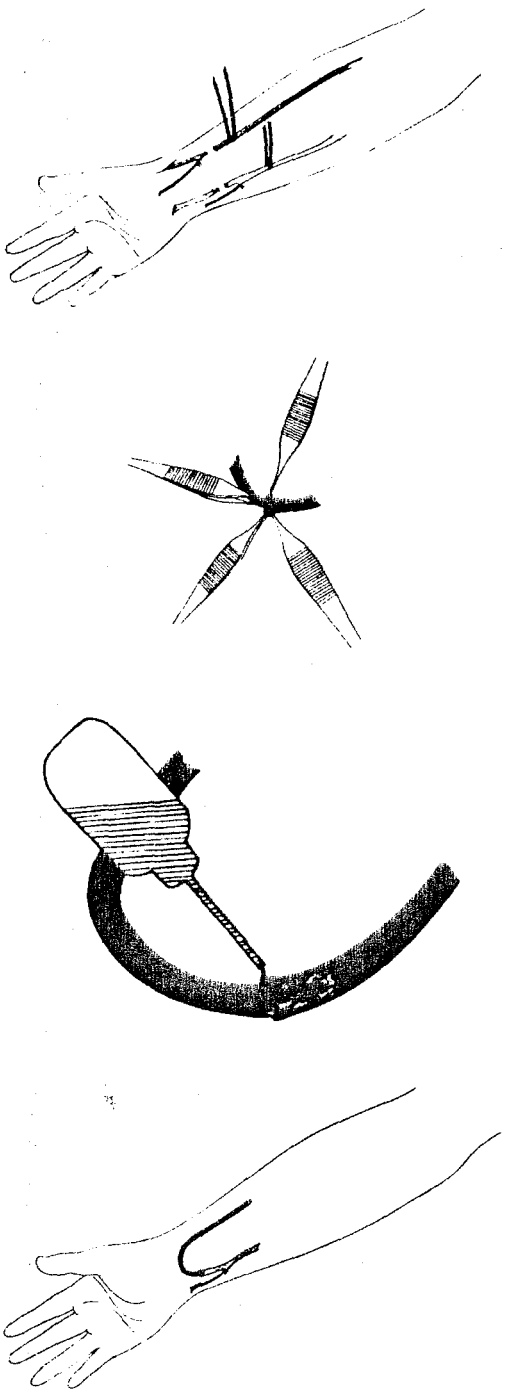

Figure 4.3 : Preparation of arteriovenous fistulae without sutures (3).

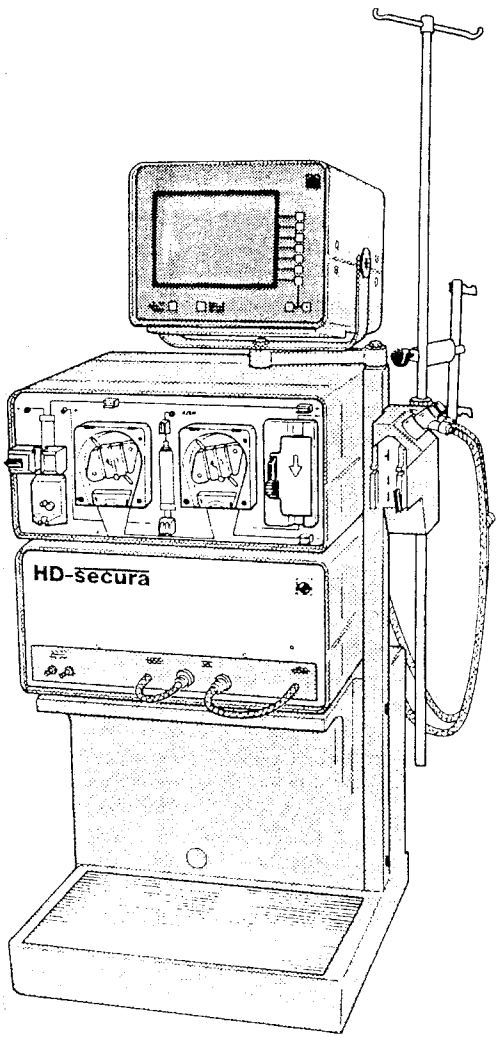

Figure 4.4.1 : A hemodialysis machine (22).

Blood pump maintains extracorporeal blood flow rates up to 600mL/min. Actual flow rates may differ by up to 10%. Blood pumps maintain net positive pressure in the blood chamber.Dialysate pumps maintain flow at 500mL/min. Negative subatmospheric pressure is generated by the dialysate pump located distally to the dialyser.

Additional key components include a vacuum pump to remove dissolved air from the diluting water prior to proportioning, a photocell system to detect effluent dialysate for blood in the event of membrane pinhole leaks or ruptures. There is an additional heparin pump in the unit for maintaining a certain level of heparin in the patient's blood to avoid clotting of the blood. The amount of heparin given to the patient can be different depending on some clinical factors(3,14).

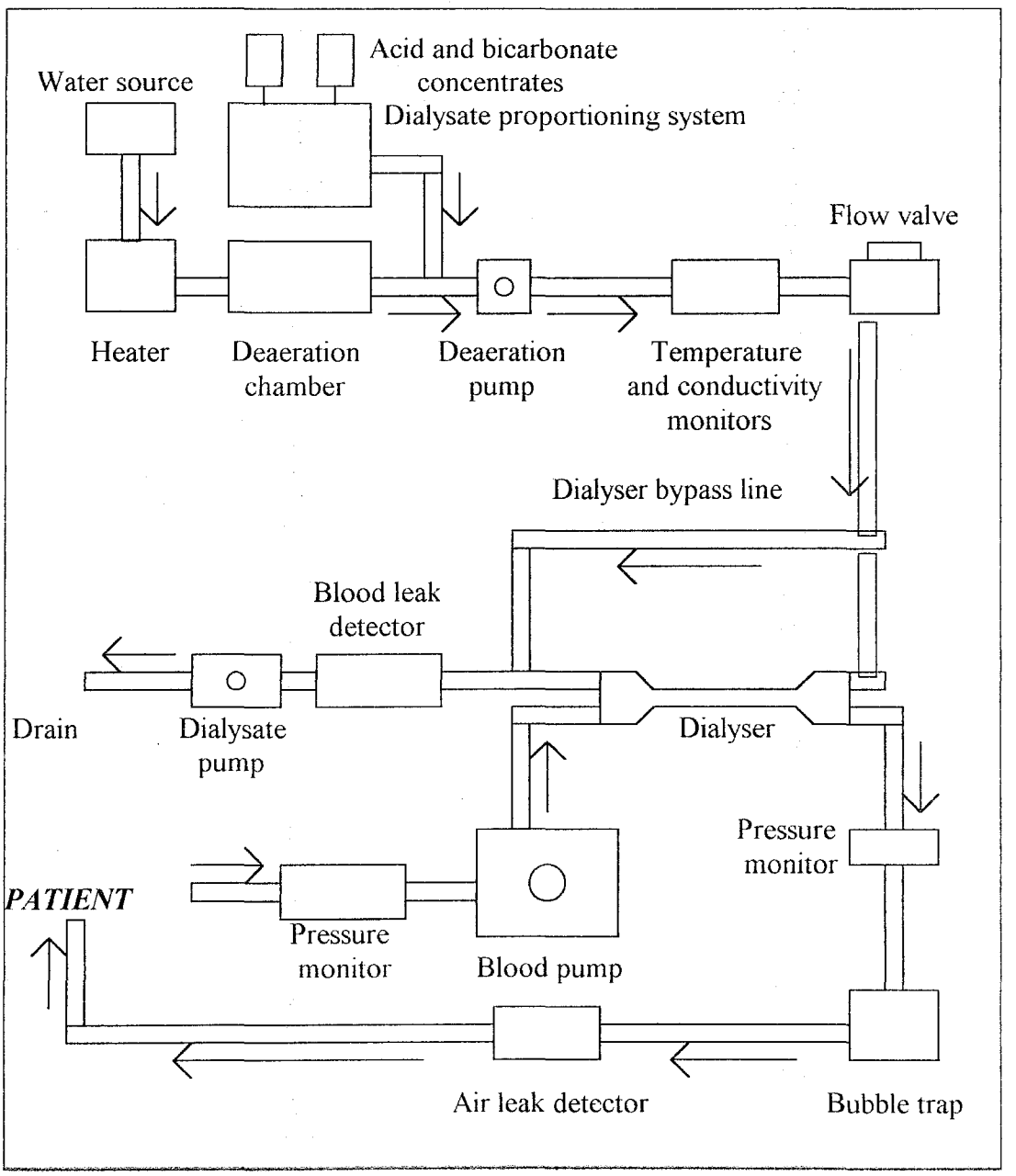

Figure 4.4.2: Basic components of a hemodialysis machine(1).

The term ultrafiltration is used for the amount of water with (electrolytes), that moves across the membrane from blood to dialysate.It is easier to explain this with an example

Interdialytic weight difference: 2000 g (The difference between the actual and the desired values of the patient's weight (22) .Since the weight loss is registered in quantity of fluid, the unit can also be given in milliliters)

Dialysis time : 4 hours

$$\text{The ultrafiltration rate} = \frac{\text{weight loss}}{\text{time}} = 500 \text{ ml/h}$$

The computer of the machine calculates the ultrafiltration rate based on the input data. There are various types of ultrafiltration programs, that can be chosen depending on the clinical state of the patient. TMP (Transmembrane pressure) is calculated by dividing result of the previous formula to a certain factor, that depends on the dialyser used. The unit for the factor is ml/mmHg/h

$$\text{Transmembrane pressure} = \frac{\text{Weight loss}}{\text{Dialysis time x Factor}} = \frac{2000}{4\text{x } 3}$$

TMP = 167 mmHg

The dialysis unit determines the venous return pressure in the blood line system, calculates the necessary pressure within the dialysis fluid and automatically compensates pressure fluctuations. There are three important balance controls of the dialysate proportioning systems.

Sodium balance: Sodium is the predominant extracellular cation, that is the main determinant of extracellular osmolarity in the form of NaCl, whereas the sodium concentration in the extracellular space is only about 7% of that in the extracellular space. A lower concentration of sodium in the dialysis fluid than that in the blood leads to a decrease in the blood volume. Another side effect of the decreased sodium concentration is the so called "Disequilibrium Syndrome", which causes edema of the brain leading to death of the patient. Vice versa, if the sodium concentration in the dialysis fluid is greater than that of blood, there will be an overhydration of the patient leading to hypertension and edema(6).

Potassium balance: Potassium is the predominant intracellular cation. If there is a disorder in the potassium level of the patient, it may lead to cardiac arrhythmias like ventricular extrasystoles, sinus tachycardia, atrial fibrillation(6). The dietary intake of potassium is also restricted to avoid hyperkalemia(=potassium level of blood higher than normal)

Buffer anions: Loss of kidney function is invariably associated with acidosis. Since hydrogen ions cannot be excreted by the artificial kidney, buffer anions as acetate or bicarbonate must be added to the dialysis solution.

To prevent serious side effects like "Disequilibrium Syndrome", cardiac arrhythmias, or hypotension blood potassium and sodium level, buffer balance, mass transfer of other electrolytes and water must be optimized.

4.5 Dialysers

As mentioned before the dialysis system is consisting of two basic components: the dialyser, which contains a semipermeable membrane and the supporting pumps with appropriate monitoring devices. Blood flow across one surface of the dialyser membrane , while physiologic dialysate is passed in opposite direction to the blood flow on the other side of the membrane.(Figure 4.5.1) Exchange of water and solutes occur across pores on the semipermeable membrane. The choice of a dialyser and determination of dialysate composition are therefore the two essential components of hemodialysis prescription.

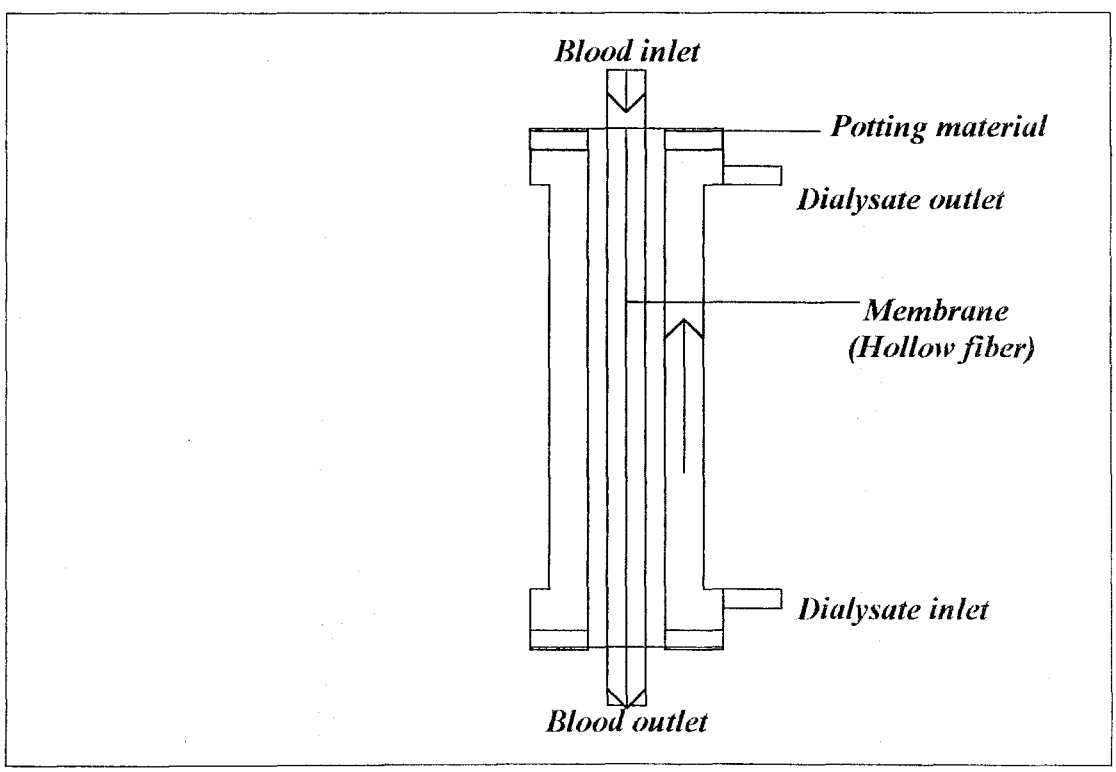

Figure 4.5.1: Cross section of a dialyser.

The hollow fiber dialysers are most commonly used. The semipermeable membrane is made of thousands of thin fibers bundled together and encased in a polyurethane container. Blood flows inside the fibers whereas the dialysate flows around their outer surface .The

dialysers are compact, easy to handle, and amenable to sterilization and reuse. Blood compartment volume is fixed. The dialysers can tolerate very high trans-membrane pressures up to 500 mmHg.

Ultrafiltration: The movement of fluid under hydrostatic pressure from the blood to the dialysate compartment is called ultrafiltration. The quantity of ultrafiltered fluid depends on the pressure difference between the blood and the dialysate compartments. This transmembrane pressure (TMP) can be controlled by varying the pressure in the dialysate or blood compartments. Increasing negative dialysate pressure will increase ultrafiltration. The plasma oncotic pressure opposes ultrafiltration. Thus fluid removes only when TMP exceeds the plasma oncotic pressure(1) . The ultrafiltration coefficient (Kuf) is a number of milliliters of fluid transferred across the membrane per hour when 1 mmHg is applied. This value varies among different membrane types.(Table 4.5.1)

Table 4.5.1: Ultrafiltration coefficient (KUf) for commonly used membranes (1):

Membrane	*Range of Kuf (ml/mmHg/h)*
Cuprophan	04 -21.4
Hemophan	20 -10.9
Cellulose acetate	2.4 -36
Polysulfonee	5.5 - 60
Polymethymethacyrlate(PMMA)	45 - 113

As pressure in the blood compartment of a dialyser usually exceeds oncotic pressure there is a certain amount of obligatory ultrafiltration associated with dialysis, which may have to be placed by intravenous fluids in the normovolemic or hypovolemic patient. The relation between ultrafiltration and KUf can be expressed as follows:

Ultrafiltration = KUf X. TMP X dialysis time (in hours)

For example, if the clinician wishes to remove 4 L of fluid during a four hour dialysis using a dialyser with KUf of 5, the TMP should be adjusted to 200 mmHg. This will give a total ultrafiltration of 4 L (5 X 200 X 4).

In practice, due to difficulties in accurate pressure measurements and variable KUfs of the same membrane under different conditions of use, it is often difficult to predict the exact amount of fluid that will be removed by the end of dialysis. Modern dialysis machines continuously measure ultrafiltrate, thus allowing for frequent adjustments and leading to a more precise removal of fluid. The published KUf is usually determined in vitro and is often an overestimate. In vivo, the KUf may be decreased due to excessive protein layering , hematocrit concentration or fiber clotting(1).

Clearance: The clearance notion in dialysers is similar to that in natural kidneys. It describes the amount of blood, that can be completely cleared of a given solute in a unit time. Thus, if 100 mL of blood per minute is completely cleared of urea as it passes through the dialyser, the dialyser is

said to have a urea clearance of 100 mL/min . Urea clearance is a surrogate for the clearance of small molecules. In vivo urea clearance is about 80% of the manufacturer's published value. Vitamin B12 is a surrogate for the clearance of middle molecules.(Figure 4.5.2) In general synthetic membrane dialysers have a higher clearance of middle and larger molecules than cellulose-based dialysers(1).

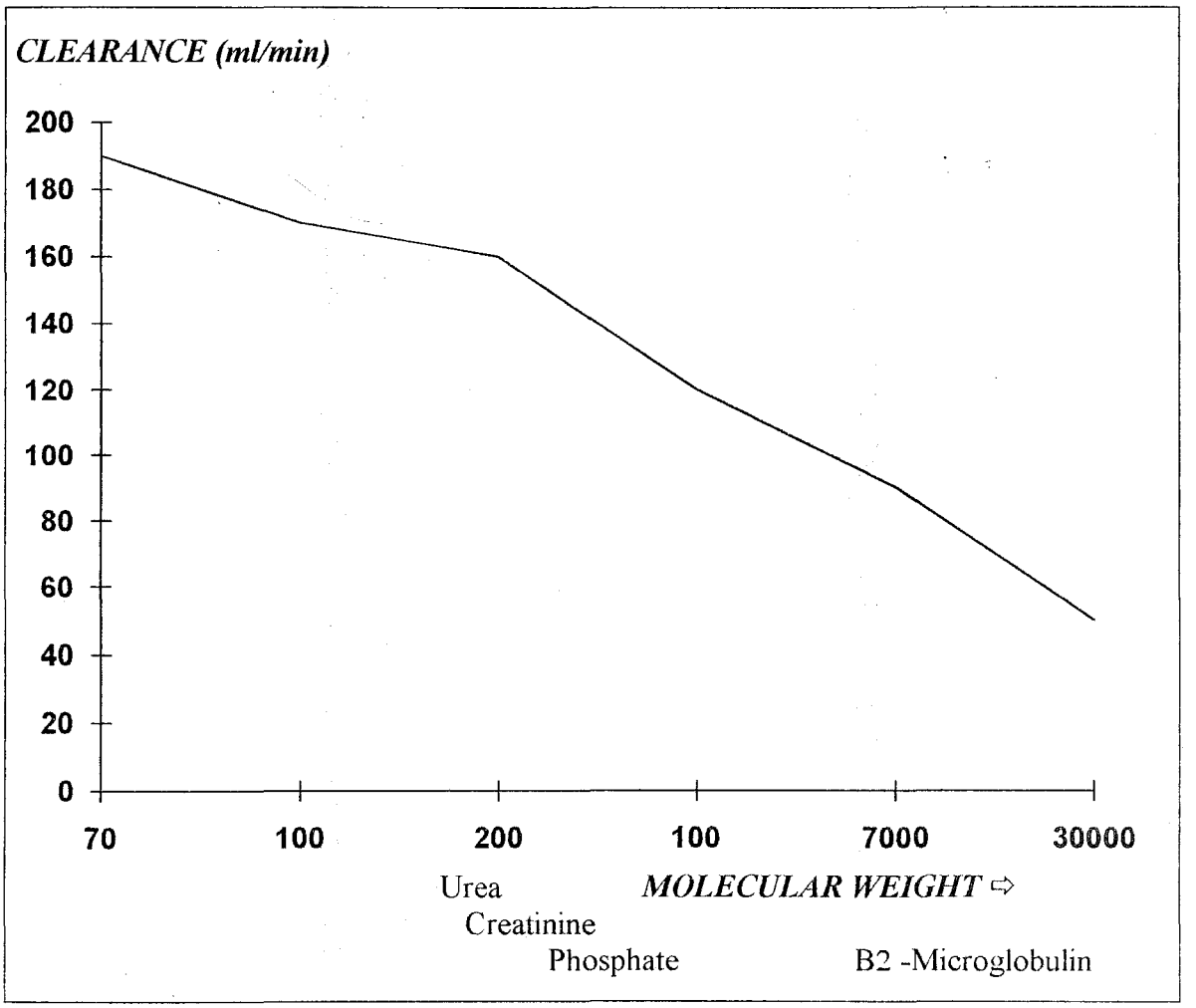

Figure 4.5.2: In vivo obtained clearances with a hollow fiber membrane(6).

Clinically, clearance can be derived by measuring blood flow (QB) and concentrations of the solute at arterial (AC) and venous (VC) ends of the dialyser using the following equation:

$$Clearance = QB \{ (AC - BC) / AC \}$$

Ultrafiltration adds to the clearance value , particularly for larger solutes, as it is associated with further solute clearance through convection. Clearance is also increased as blood and dialysate flow rates are increased.This effect is most marked for small solutes such as urea and is less for larger solutes . Both blood and dialysate form a thin layer on each side of the semipermeable membrane, which solute molecules have to cross before reaching the other side

of the membrane(1). Increasing blood and dialysate flow helps in diminishing these layers. Different membrane types have their own urea clearance values.(Table 4.5.2)

Table 4.5.2: Urea clearances for commonly used membranes at 200 mL/min blood flow(1)

Membrane	*Range of Urea Clearance (mL/min)*
Cuprophan	50-196
Hemophan	82-194
Cellulose acetate	128-194
Polysulfone	150-192
Polymethylmethacrylate(PMMA)	169-194

Dialysate flow above 500mL/min does not result in a significant increase in clearance. Any gain in clearance is seen with increasing flow is due to improved dialysate distribution by eliminating nonuniform distribution. (Figure 4.5.3)

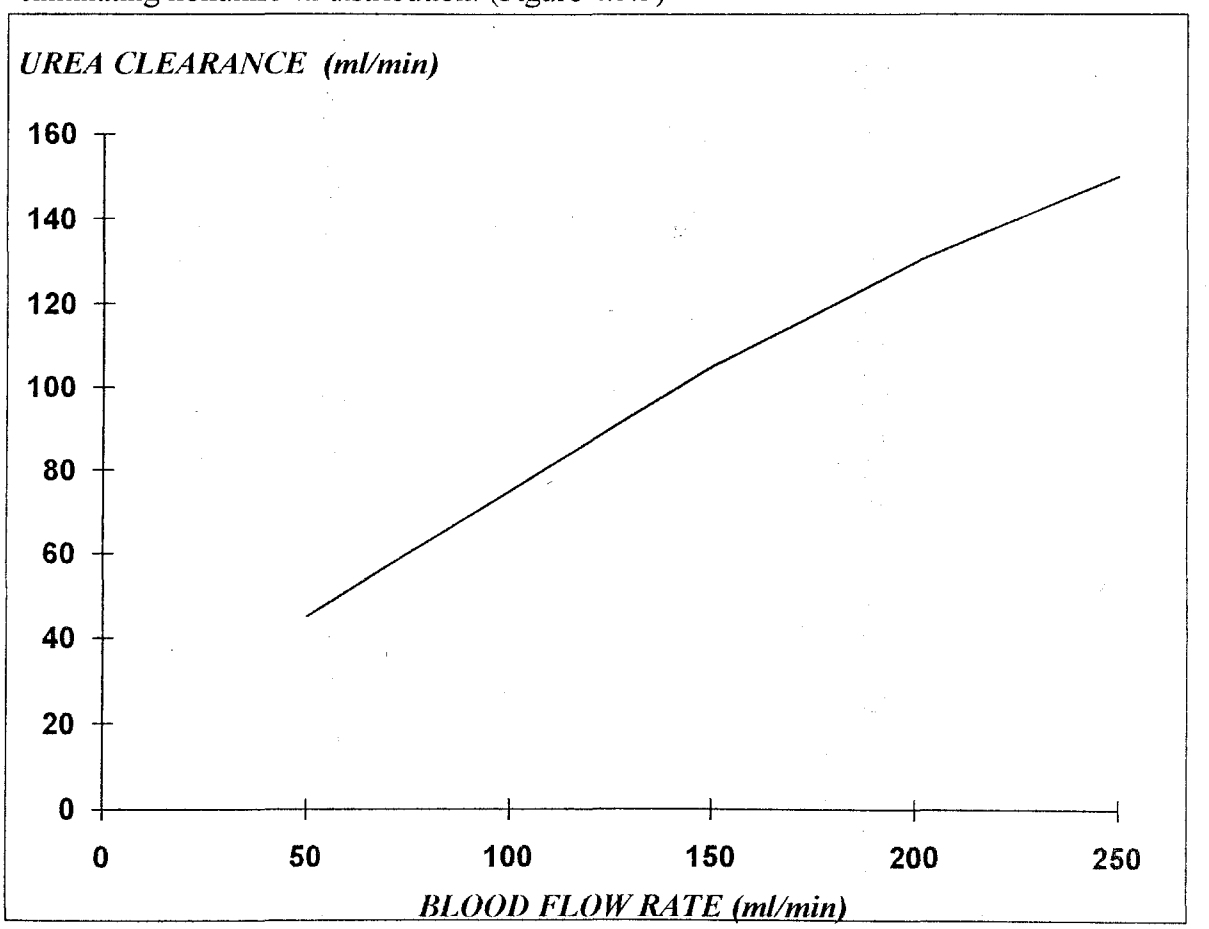

Figure 4.5.3: In vivo urea clearance with a hollow-fiber Cuprophan dialyser(6)

Treatment conditions and membrane properties affect clearance of solutes differently, depending on their molecular weight(Table 4.5.3).

Table 4.5.3: Dialysis conditions with effect on clearance (18).

Increasing	*Effect on clearance* LMW solutes (<200 d)	HMW solutes (>1000 d)
Blood flow rate	Increases	Little or no effect
Dialysate flow rate	Little effect	Little or no effect
Membrane surface area	Little effect	Almost linear increase
Membrane permeability	Little effect	Almost linear increase

LMW - low molecular weight
HMW- high molecular weight

The mass transfer coefficient KoA represents the ability of a solute to pass through the pores of a dialyser . The higher this value , the more permeable is the membrane ..The combination of KoA and high blood flow will increase clearance of both small and large molecules (1).

4.5.1 Possible Dialyser Improvements

The attempts to improve the quality and hemocompatability of the dialysers improves the life quality of the ESRD patients.There are many ways to improve the dialysers:(Figure 4.5.1.1)

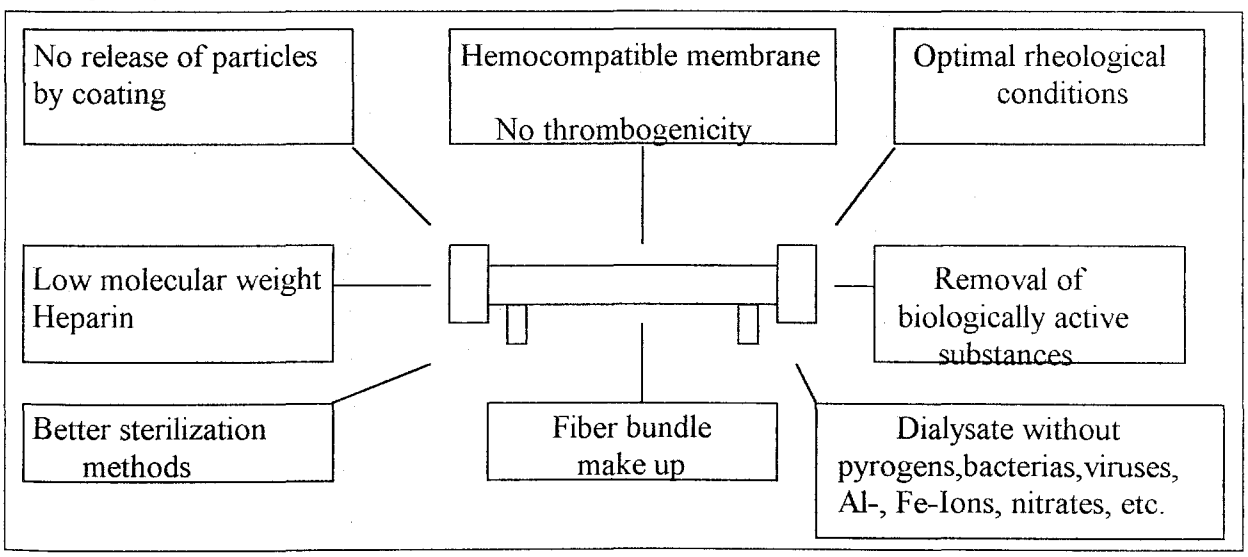

Figure 4.5.1.1: Possible dialyser improvements (15,18).

We will be focusing on the membrane,which is the most important part of the dialysis procedure. An ideal membrane should have the properties described in Figure 4.5.1.2 .

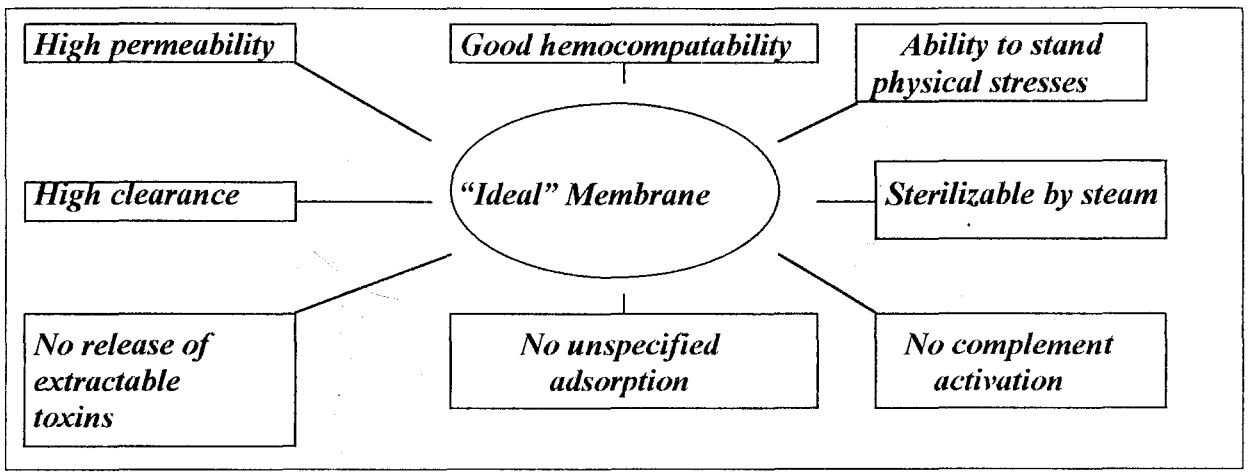

Figure 4.5.1.2: The properties of an "ideal" dialysis membrane(15,18).

The membrane is consisting of a large number of elliptical pores , formed by the gaps in the molecular structure.(Figure 4.5.1.3)

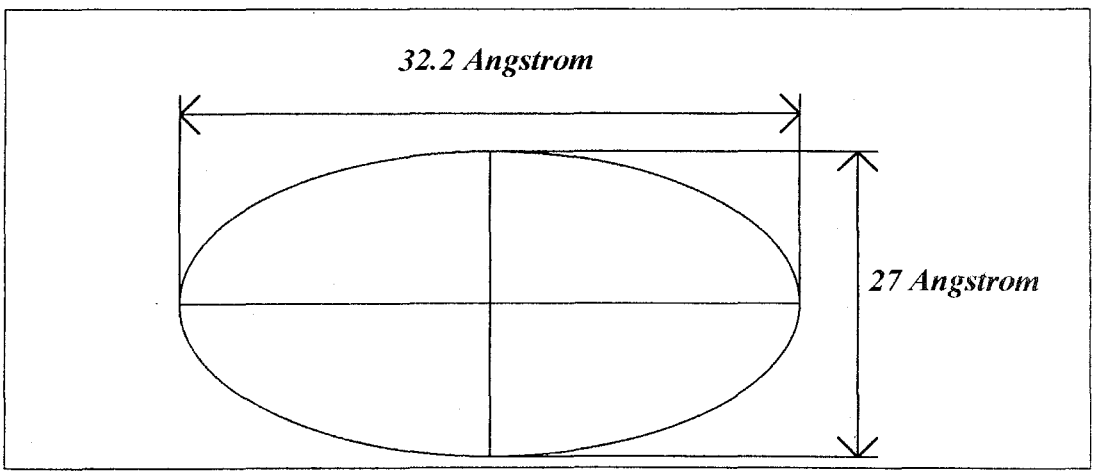

Figure 4.5.1.3: The best fit pore size in its unstrained state(6).

The most effective way of increasing the solute permeability is to pre strain the membrane in the weak direction by about 15% as this would increase the size of the minor axis from 28 Angstrom to 40 Angstrom with a little change to original major axis(6).The predicted effect on membrane permeability for a range of molecular sizes is shown in Figure 4.5.1.4.

The dialysis membrane represents the largest surface in the complete extracorporeal circuit. As mentioned before biocompatability and the mechanical stability are prominent features in addition to permeability profiles.

Most efforts to improve the strength of the membrane had no outcome , because two objectives of the membrane function are incompatible with this aim(6).

-Methods that improve the permeability of the membrane, unfortunately degrade the mechanical properties.

-Modifications, that increase the strength, decrease the permeability of the membrane.

The mechanical stability of the membrane is important in preventing blood leaks or broken fibers during dialysis. This issue is much more important in centers, where the dialysis membranes are reused(1).

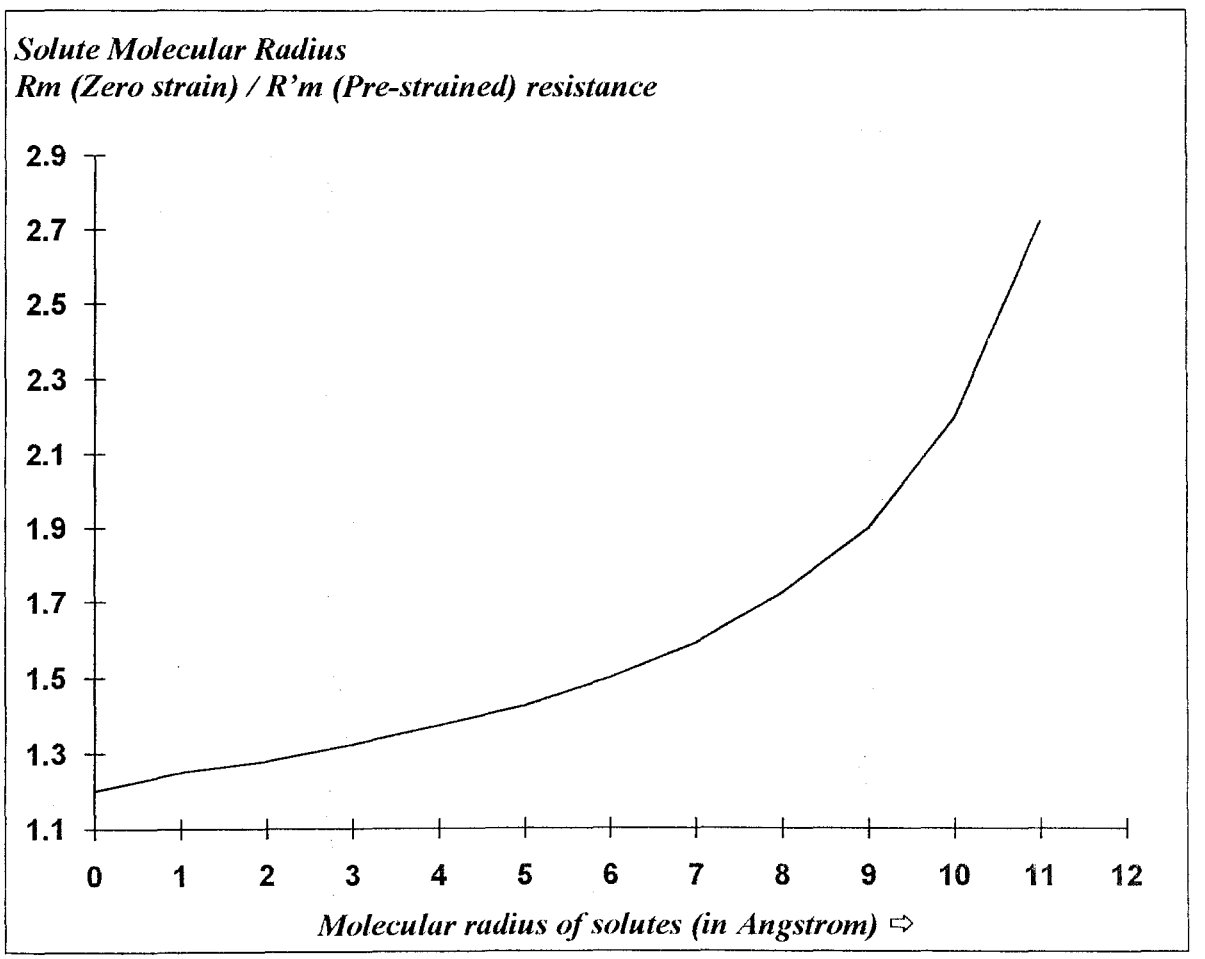

Figure 4.5.1.4: Predicted effect of 15% strain in the weak direction on the solute permeability of a cuprophan membrane as a function of solute molecular radius r (for urea r = 2.8 Angstrom,for creatinine r = 3.6 Angstrom,for Vitamin B12 r = 8.3 Angstrom) (6).

4.5.2. Dialyser Membrane Materials

As a foreign object, the dialyser elicits a variety of responses from the patient's body. During hemodialysis , plasma proteins (e.g., complement) and blood cells (e.g., leukocytes and platelets) are activated because of the interaction of blood with the dialysis membrane (1). These activated products cause a variety of clinical events. Alternatively, the dialyser may release substances (e.g., ethylene oxide) that are directly toxic to the body. Bioincompatability of a dialyser has of acute and chronic effects. The acute effects are often severe, but the more subtle and chronic effects also have significant impact on dialysis patients. In addition to the dialysis membrane, other components of the extracorporeal circuit, such as the tubing, are also important , but these issues will not be discussed here(1,16,18).

The most commonly used dialysis membranes are listed in Table 4.5.2.1. Dialysis membranes are generally classified into cellulosic and noncellulosic types. The noncellulosic ones are synthetic polymers and are generally more expensive. The term ***high-flux membrane*** refers to a membrane with a high ultrafiltration rate and does not necessarily imply high urea clearance. ***High-efficiency membrane*** on the other hand, refers to those with high urea clearance and usually large surface as well. A dialyser can be high-flux or high-efficiency or both (1,5,9).

The classical membranes being used for hemodialysis since more than a quarter of a century are the membranes made of regenerated, unmodified cellulose. This group includes SCE, an unmodified cellulosic membrane, which can be obtained by the saponification of the cellulose ester, cellulose acetate. The material obtained as a result from this saponification, is similar to standard regenerated cellulose(16) .

Among all membranes from regenerated cellulose , Cuprophan has the biggest market share and more than 400 million dialysis treatments have been performed with this membrane.

Membranes from regenerated cellulose are currently under attack because of their lack in biocompatability. With the advent of synthetically modified cellulose membranes and synthetic membranes , the general perception of cellulose membranes as being incompatible has to be reconsidered(16,23).

Table 4.5.2.1. Membrane composition of commonly used hemodialysers(16).

Cellulose based membranes

Unmodified
- Cuprophan
- Bioflux
- Regenerated cellulose
- Saponified cellulose ester (SCE)
- Cellulose

Modified
- Cellulose-acetate
- Cellulose-diacetate
- Cellulose-triacetate

Surface coated
- Biomembrane
- PEG-Cellulose

Synthetically modified
- Hemophan (+DEAE)
- SMC (+Benzyl)

Noncellulosic (synthetic polymers)

- Polyacrylonitrile (PAN)
- Polysulfonee
- Polymethlymethacrylate (PMMA)
- Polycarbonate
- Ethylvinylalcohol copolymer (EVAL)

The modified cellulosic membranes exhibit a biocompatability pattern comparable to synthetic polymers. Synthetically modified cellulose membranes can be obtained by means of a chemical change of cellobiose, the molecular unit of the cellulosic polymer(Figure 4.5.2.1) .

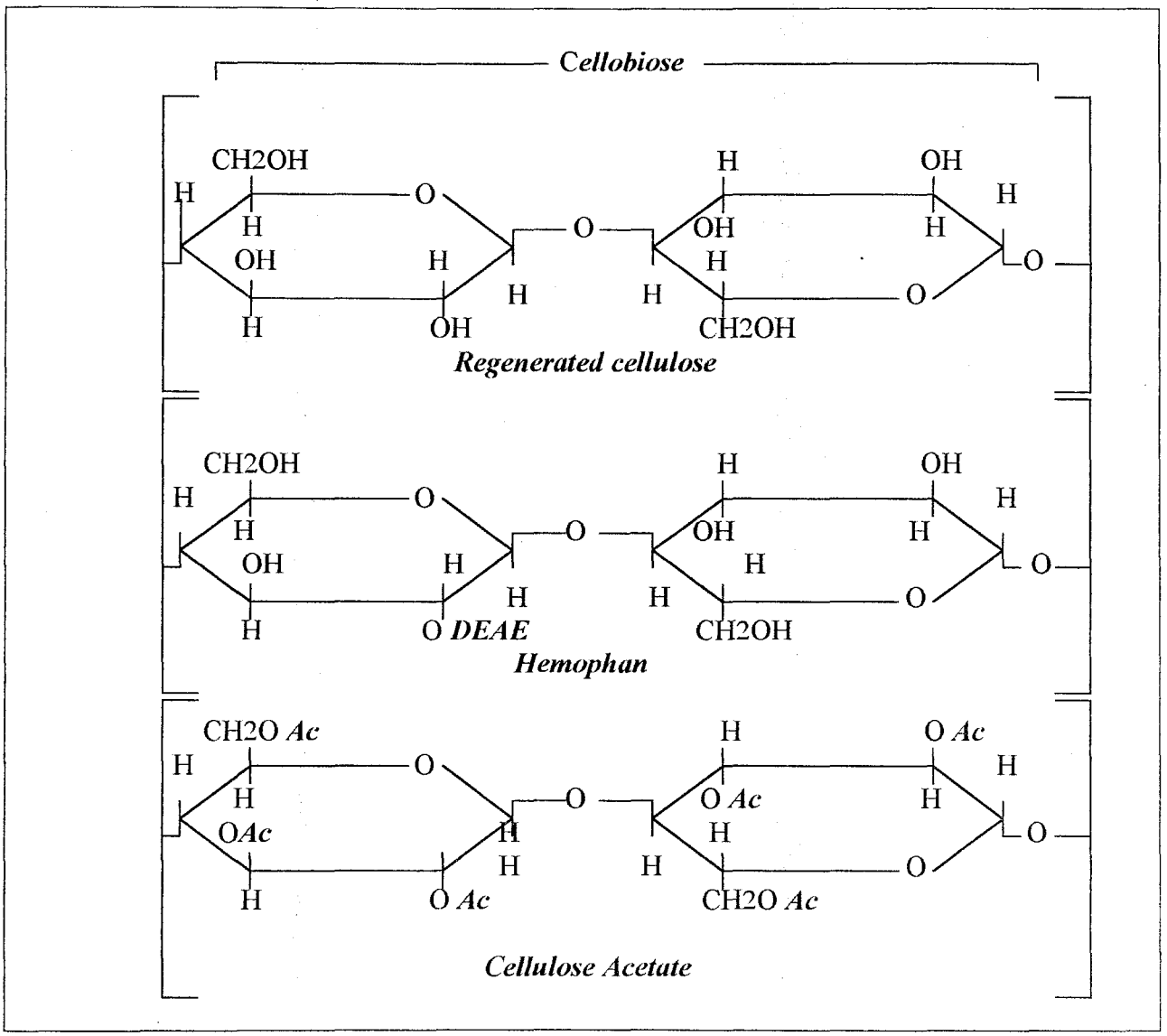

Figure 4.5.2.1 : Chemical modifications of the basic glucose unit of cellulose(18).

Cellobiose consists of two glucose molecules, which are connected in a 1.4 ß-glucan configuration(16). The glucose molecule contains three OH-groups, which can be easily submitted to chemical reactions by :

1. Etherification with either DEAE-groups (Hemophan), benzylgropus (SMC) or chain grafting with polyethyleneglycol (PEG-RC).

2. Esterification by acetyl groups or others.

3. Surface-coating with synthetic polymers.

As a result of these modifications , most of the known biocompatability parameters improved considerably, as it was shown in a variety of controlled clinical studies with synthetically modified cellulosic membranes(16).

The second main group of dialysis membranes consists of synthetic polymers and is divided into four smaller groups. Four smaller groups are useful to describe the different techniques for hydrophilisation(16,27). Typical synthetic polymers for dialysis membranes are hydrophobic by nature and have to be rendered hydrophilic to be used as a filter for blood toxins.

Only membranes from ethlyvinylalcohol copolymers (EVAL) are hydrophilic by nature and can be used without alteration as filter materials. Membrane biocompatability and performance depends on these hydrophilisation processes. Complement activation observed with polysulfone membranes depends on certain hydrophilic additives, such as polyvinylpyrrolidon (PVP) and bradykinin generation by polyacrylonitrile (PAN) membranes depending on the components used for its copolymerisation(16).

Several techniques can be used for hydrophilisation. Polymers are either blended with hydrophilic components, such as polyethyleneglycol (PEG) or they are copolymerised during or after the extrusion of the membrane capillaries.

The development of highly permeable polysulfone membranes was described by Streicher and Schneider in 1985. Göhl et al described development and manufacturing of polycarbonate membranes (16).

First clinical studies with AN69 PAN membranes were published by Funck-Brentano et al and showed a high permeability to middle molecules. Krieter et al presented a PAN membrane , which is chemically different from AN69 PAN . His data show that a SPAN-membrane did not generate bradykinin and blood pressure drops in a sheep model(16).

Finally , Schaefer et al, demonstrated, that the new low-flux polsulfone membrane had similar biocompatability characteristics as the synthetically modified cellulosic membranes(16).

The following points need to be emphasized:

1. Cellulosic membranes can either be high-flux or low-flux; the same is true for synthetic membranes(1).

2. An obvious corollary is that neither all cellulosic membranes can be regarded as the same , nor all synthetic membranes can . Although two membranes are made of the same material, they can be quite different due to possible different manufacturing techniques(1).

3. The biocompatability characteristics may differ among cellulosic membranes as well as among synthetic membranes. Although synthetic membranes are usually considered to be more biocompatible than those of cellulosic ones, this kind of generalization is always not true. Biocompatability certainly depends on specific criteria proposed by experts(1).

Since the beginning of the dialysis as a standard therapy , classical cellulosic membranes have become thinner and thinner. As membrane thickness governs also its permeability properties, the overall membrane area needed to achieve a defined clearance also becomes smaller(Figure 4.5.2.2 and 4.5.2.3).

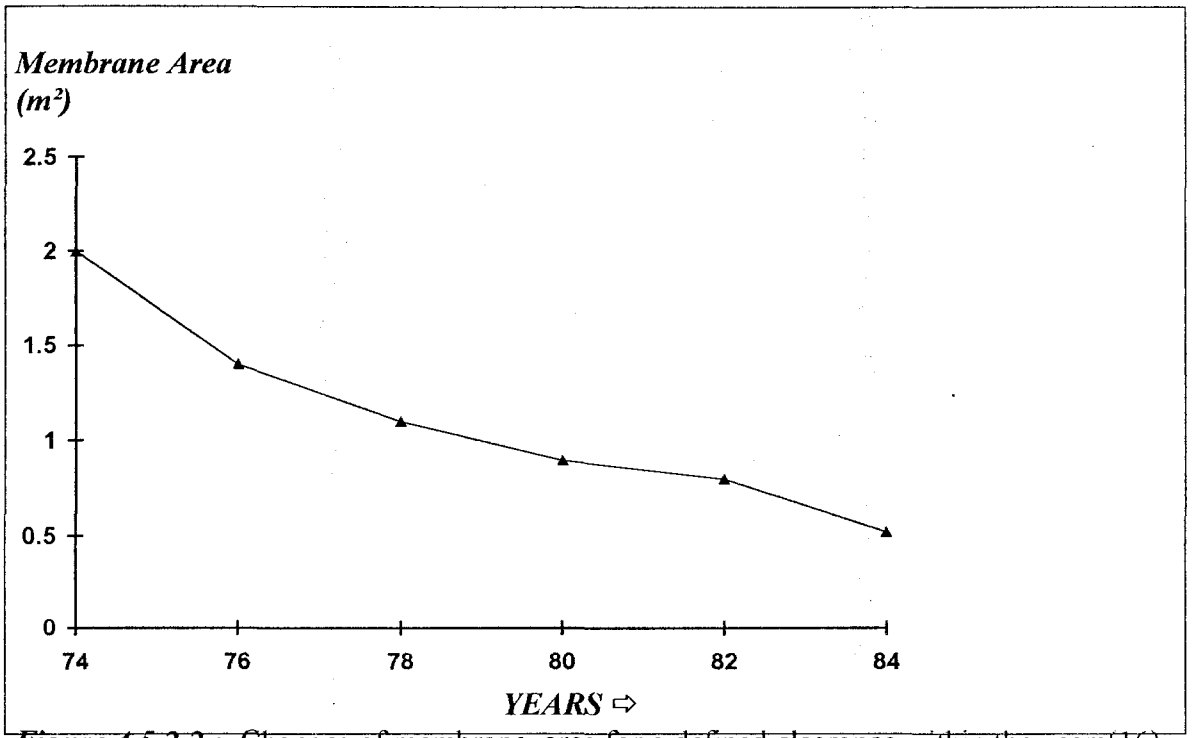

Figure 4.5.2.2 : Changes of membrane area for a defined clearance within the years(16).

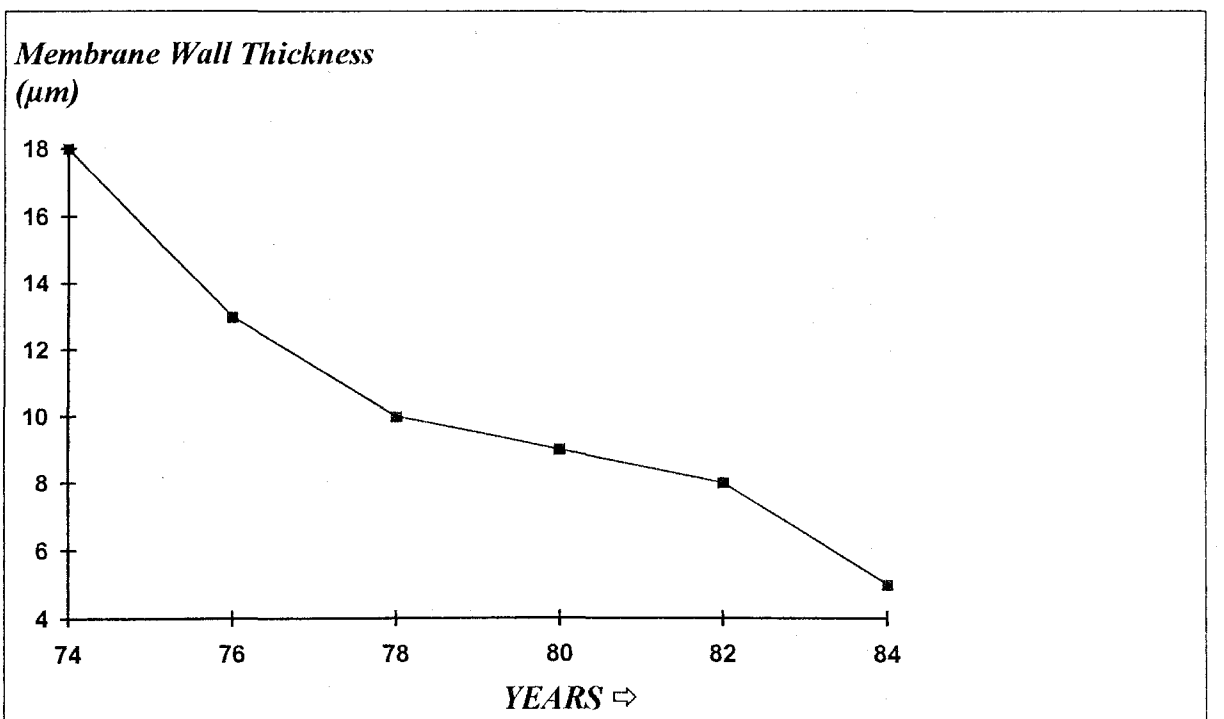

Figure 4.5.2.3 : Changes of membrane wall thickness (μm) for a defined clearance within the years (16).

Urea clearance = 150 ml/min
QB (Blood flow rate) = 200 ml/min
(Diaysate flow rate) = 500 ml/min

are kept constant in Figures 4.5.2.2 QD and 4.5.2.3.

4.5.3.Membrane Transport and Removal Characteristics

The removal of uremic toxins from the bloodstream follows three mechanisms:

1. Small molecules up to a molecular weight of about 5000 diffuse from the bloodstream to dialysate through the membrane along their concentration gradient , according to ***laws of diffusion***. The diffusive permeability of a membrane is defined as the ratio between the diffusion coefficient and membrane thickness. The reduction of the membrane thickness leads to a better clearance. As a result it is possible to use smaller membrane surface areas in order to achieve a defined dialyser clearance. Figures 6.5.2.2 and 6.5.2.3 show the historical trend towards smaller membrane thicknesses for cellulosic membranes and appropriate membrane areas needed for a urea clearance of 150 ml/min . In 1975 a dialyser, containing a 16 µm cuprophan membrane, had to have a membrane surface area of 1.6 m^2 as compared to only 0.52 m^2 for a dialyser with a membrane of 5 µm in 1984. Dialysers with ultrathin membranes of that type and large surface areas enable manufacturers to produce high efficiency dialysers with low-flux membranes and a KuF of > 10 ml/mmHg h (16) .

2. A second mechanism controlling the transport of uremic toxins through the membranes is ***convection***. Conventional transport only depends on the pressure difference between blood and dialysate side of the membrane and influences mainly the transport of large molecules (16).

3. A third parameter adds to the removal characteristics of dialysis membranes : ***adsorption***. Blood proteins, uremic toxins and drugs administered during dialysis can be adsorbed on to the surface of dialysis membranes mainly of synthetic origin. Adsorption can either be induced by interactions of positive and negative charges or by the means of Van der Waals-forces. This mechanism has gained increasing attention in recent years as ß2-microglobulin , complement proteins, erythropoietin, fibrinogen, coagulation factors, anticoagulants and endotoxins can be removed by either specific or nonspecific adsorption (16).

4.6. Blood Tubing

The blood tubing consists of the blood set and an air trap(Figure 4.6). It is connected to dialysis needles, which are available in different sizes. The most common sizes are 15, 16 and 17 gauge needles. The high blood flows necessary to perform high-efficiency and high-flux dialysis require the use of larger 15-gauge needles(1).

The required volumes of the blood tubing 150 mL for adults , 56 for pediatric patients and 18 mL for neonates.

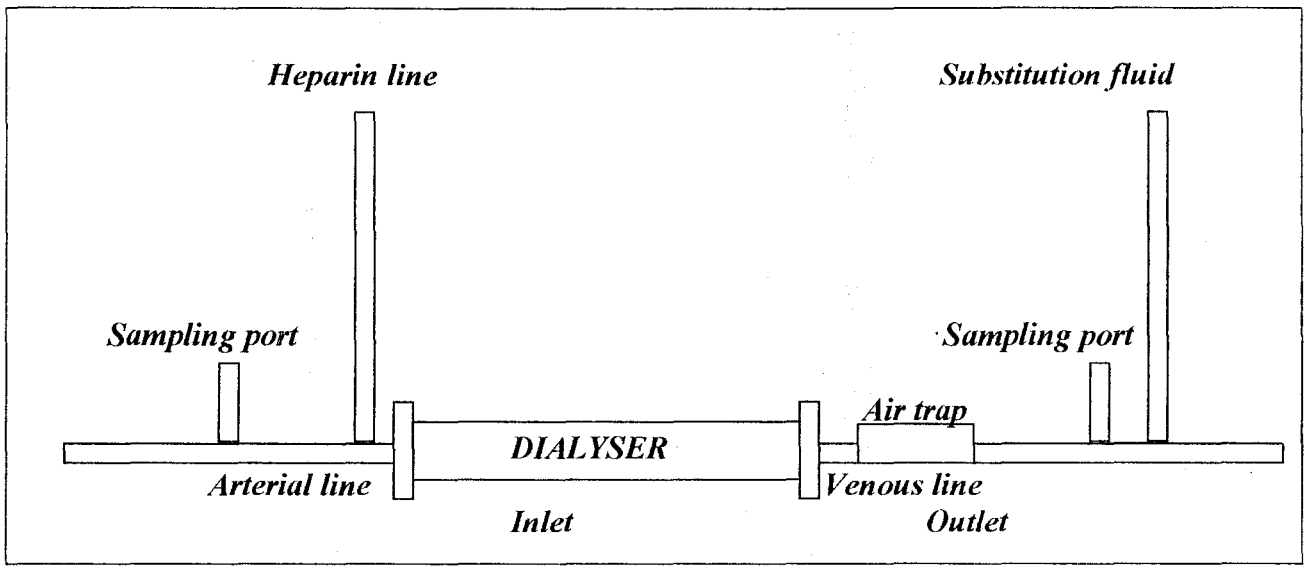

Figure 4.6 : Blood tubing for hemodialysis (1).

One precaution, that should be observed in monitoring blood flow, is the flow rate is based on the volume of the adult tubing (150 mL) . If a different tubing is used, the actual flow rate should be calibrated (1).

4.7. Hemodialysis Solutions

The hemodialysis machine uses acetate solutions and acetate solutions mixed with bicarbonate solutions . These solutions produced in Turkey by private companies and SSK are preserved in special containers. The hemodialysis machine has a proportioning unit, which mixes these solutions with the water coming from the water treatment system.(Figure 4.7) The liquid after this proportioning procedure is called dialysate(1).

The bicarbonate solutions contain 84 g of sodium bicarbonate/L.
The acidic bicarbonate concentrates contain the following in every liter:

Sodiumchloride	214.8 g
Potassiumchloride	2.612 g
Calcium chloride. 2H2O	7.72 g
Magnesium chloride. 6 H2O	3.558 g
Acetic acid (99-100%)	4.207 g

If one liter acidic bicarbonate solution containing 84g sodium bicarbonate /L , 32.775 L pure water and 1.225 L concentrated basic bicarbonate solution is used the following dialysate solution will be obtained:

Na+	140 m mol/L
K+	1m mol/L
Ca++	1.5 m mol/L
Mg++	0.5 m mol/L
Cl -	110 m mol/L
CH3COO -	0 m mol/L
HCO3 -	33 m mol/L
Osmolarity	288 m osm/L

There are also special solutions for individual patient's needs. For example , there are solutions , which contain no potassium , for patients whose blood potassium level is high.

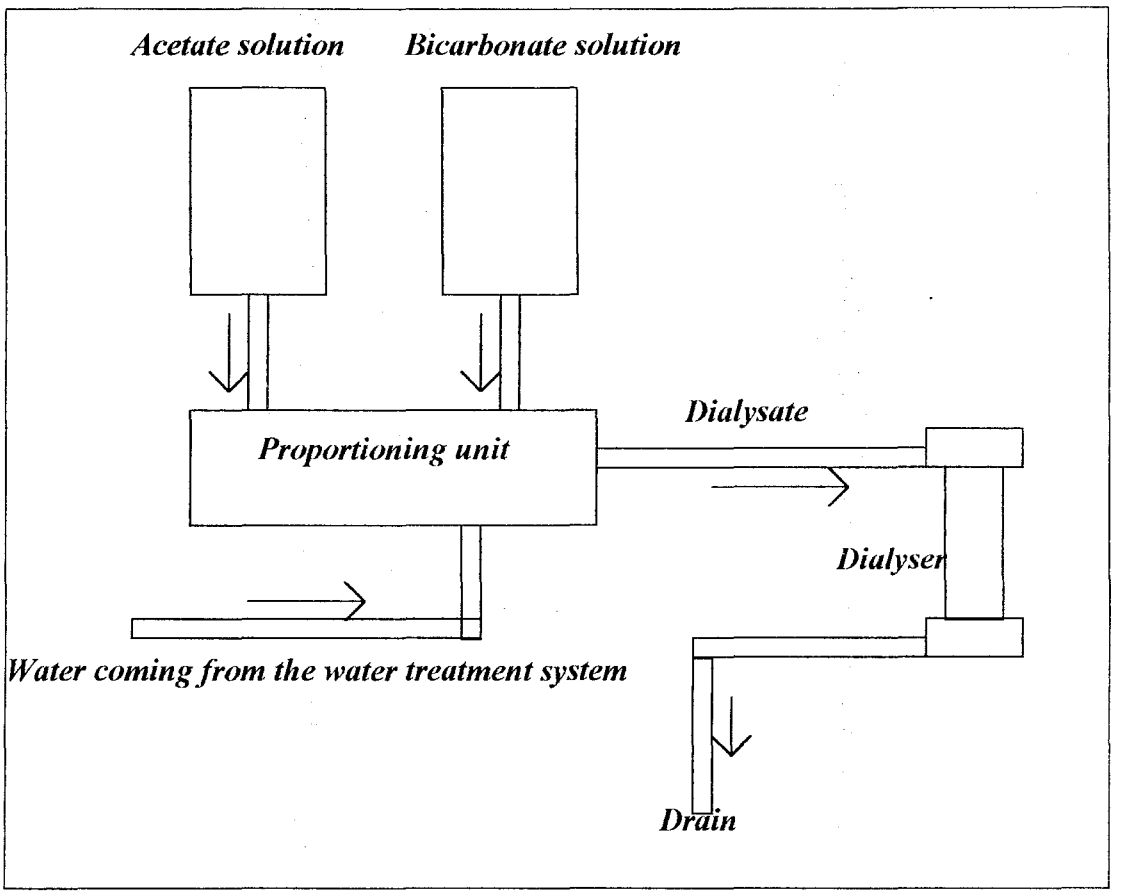

Figure 4.7. Schematic diagram of the dialysate preparation in a hemodialysis machine.

4.8. Anticoagulation

Although the concept of hemodialysis had been well described , chronic hemodialysis became feasible only after the discovery of heparin in 1926. With the advent of more efficient artificial dialysers , that require smaller blood volumes than their predecessors do, heparin requirements have diminished (1).

Recently it has been shown, that acute dialysis may be performed without anticoagulation and with minimal complications in patients , for whom heparin administration can be dangerous.

A high-risk patient is defined as one, who has undergone surgery within the last three days or has blood loss, a recent head trauma or a bleeding diathesis. The anticoagulation for

dialysis should be adjusted to prevent clotting in the dialysis apparatus without provoking or exacerbating bleeding.

Several techniques of anticoagulation are currently available:

1. Heparinization

   - Systemic
   - Controlled
   - Tight
   - Regional

2. Use of heparinoids, prostacyclin and regional citrate

3. No anticoagulation

An ideal anticoagulation for hemodialysis does not yet exist, but heparin is the main anticoagulant therapy. There are various protocols with their benefits and limitations. (Table 4.8).

No single anticoagulant regimen is suitable for every hemodialysis procedure, patients undergoing hemodialysis must be periodically evaluated by the physicians for risks of bleeding and the appropriate anticoagulation regimen should be selected according to this assessment (1,10).

Table 4.8: Protocols of coagulation for hemodialysis(1).

Type of coagulation	*Indication*	*Advantages*
Systemic heparinization	No risk patient	Prevents extracorporeal clotting
Controlled heparinization	Moderate risk patient	Less heparin usage
Tight heparinization	High-risk patient	Minimizes heparin dosage
Regional heparinization	High-risk patient	Maintains normal clotting times
No anticoagulation	High-risk patient	No heparin given
Prostacyclin	High-risk patient	No heparin given
Heparinoids	Low- to moderate risk patient	Less systemic anticoagulation
Citrate	High risk patient	No systemic anticoagulation

4.9. Medical Stuff Specialized in Hemodialysis

Both doctors and nurses working in the hemodialysis department should have both technical and medical knowledge about hemodialysis . The doctors have to deal with hypertension, urinary tract infections, anemia, bone problems, cardiovascular problems, neurological problems and other metabolic problems. With the help of new hemodialysis techniques and drugs, these patients can live their routine life, which was not the case 10 years ago .

One of the most important problems is the psychological state of the patient and their problems with their families. Significant percentages of ESRD patients report chronic psychological symptoms , impaired activities of daily living and social functioning. Each psychosocial problem recognized in chronic dialysis patients is assessed by the treating physicians and dialysis staff members as to its seriousness, chronicity and reversibility (1).

Anxiety syndromes and depression are two major psychological problems, that may occur in chronic dialysis patients.

Contribution of such an excellent psychosocial care is ignorable to the cost of dialysis , however it can help to the patients in resolving their marital, family and other social problems .

Achieving to the goal of rehabilitation OF ESRD patients requires the integration of excellent medical, psychosocial and psychiatric care together with occupational rehabilitation services.

There are also certain risks for the medical staff working in the dialysis department. One of these risks is possibility of becoming infected with hepatitis B and C virus. Figure 4.9 shows the rate of hepatitis B infection in the medical staff working in dialysis departments in different countries.

The rate of Hepatitis C is also increasing among the patients and the medical staff. Another problem is the HIV virus, which can infect people via blood and its products.

For these reasons certain blood tests are performed before a patient is accepted to a dialysis program. Those, who are infected with hepatitis, are treated with the other hemodialysis machines in other separated rooms.

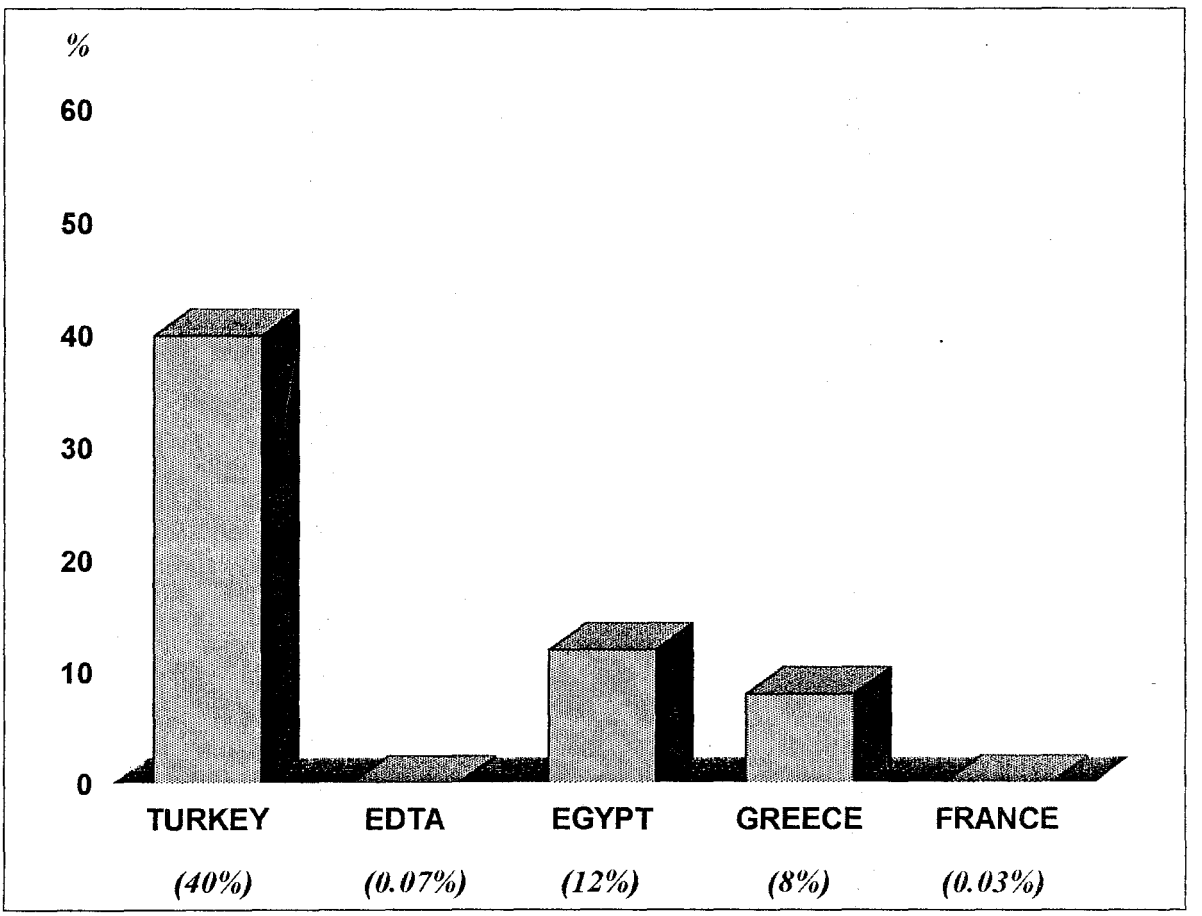

Figure 4.9: The rate of becoming infected with Hepatitis for the medical staff working in dialysis departments in different countries (20).

Most of these contaminations occurs during vascular access and catheter placements. Therefore maximum care should be taken especially by doctors and nurses during these procedures and all the medical staff working in dialysis departments should be vaccinated against these infections. All of the patients and the other staff except doctors,nurses should be specially educated about the risk of these infections and the ways of contamination .

5. EXPERIMENTAL STUDIES

The experimental studies performed consist of the following:

1. Stereomicroscopic evaluation of different dialysers.

2. Evaluation of the fibers originating from different dialysers by scanning electron microscopy (SEM) .

3. Tensile test of dialyser fibers .

4. Patient monitorisation during hemodialysis .

5. Blood tests while using different dialysers for the same patients.

The first three experiments were performed in the laboratories of Metallurgical Engineering Department of Istanbul Technical University and the last two experiments in the Dialysis Department of SSK Istanbul Hospital.

5.1. Stereomicroscopic Evaluation of Different Dialysers

The aim of this experiment was to obtain a better knowledge about the bundle configuration of normal and high flux dialysers.

Materials and Methods

The dialysers have been cut at their upper part as shown in figure 5.1.1.

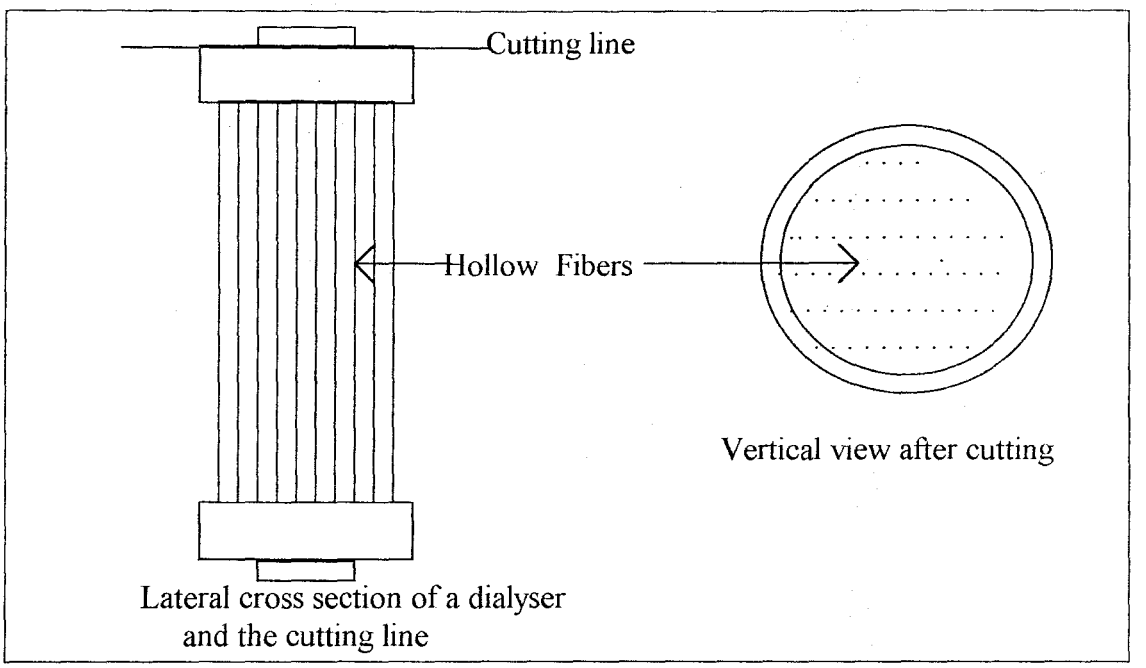

Figure 5.1.1 : Dialyser Preparation for Light Microscopy

Results

High flux dialysers were designed in such a way, so that the hollow fibers are placed very densely in the fiber bundle configuration and the membrane surface area is higher compared to low-flux dialysers by this way(Figures 5.1.2 , 5.1.3 , 5.1.4 and 5.1.5.).

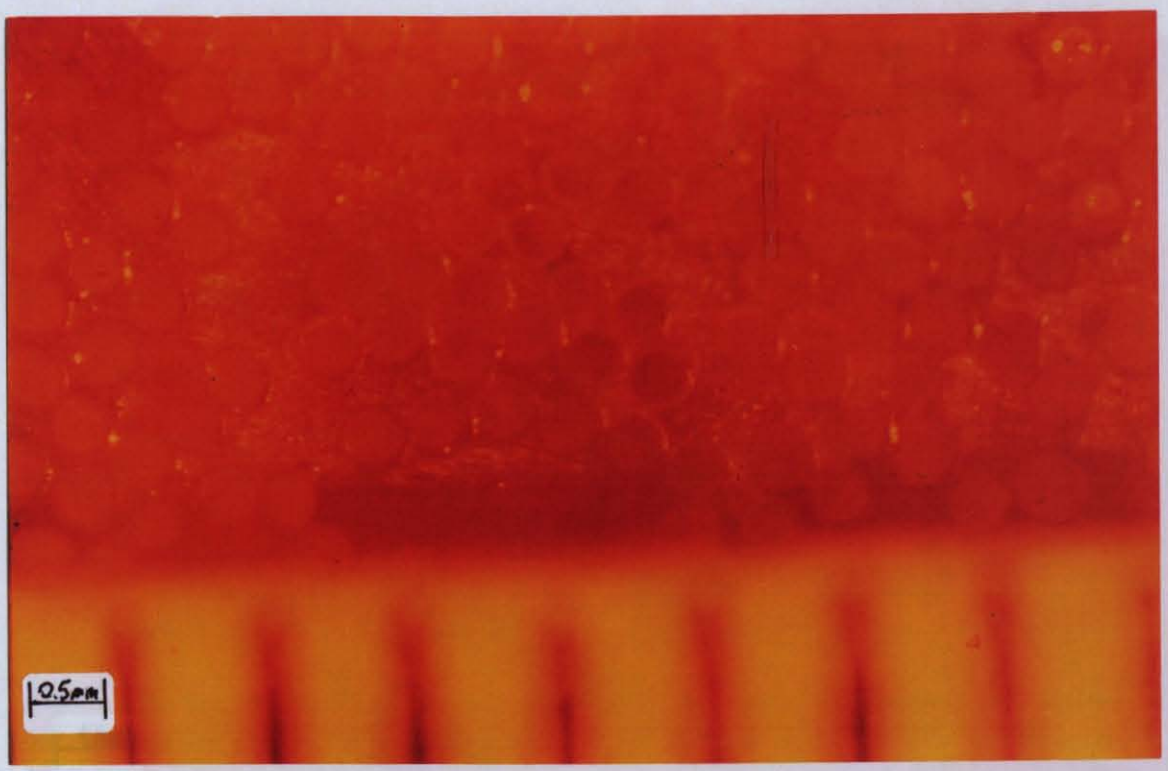

Figure 5.1.2 : Vertical view of a high-flux cellulose-diacetate dialyser fiber bundle.

Figure 5.1.3 : Vertical view of a cuprophan fiber bundle.

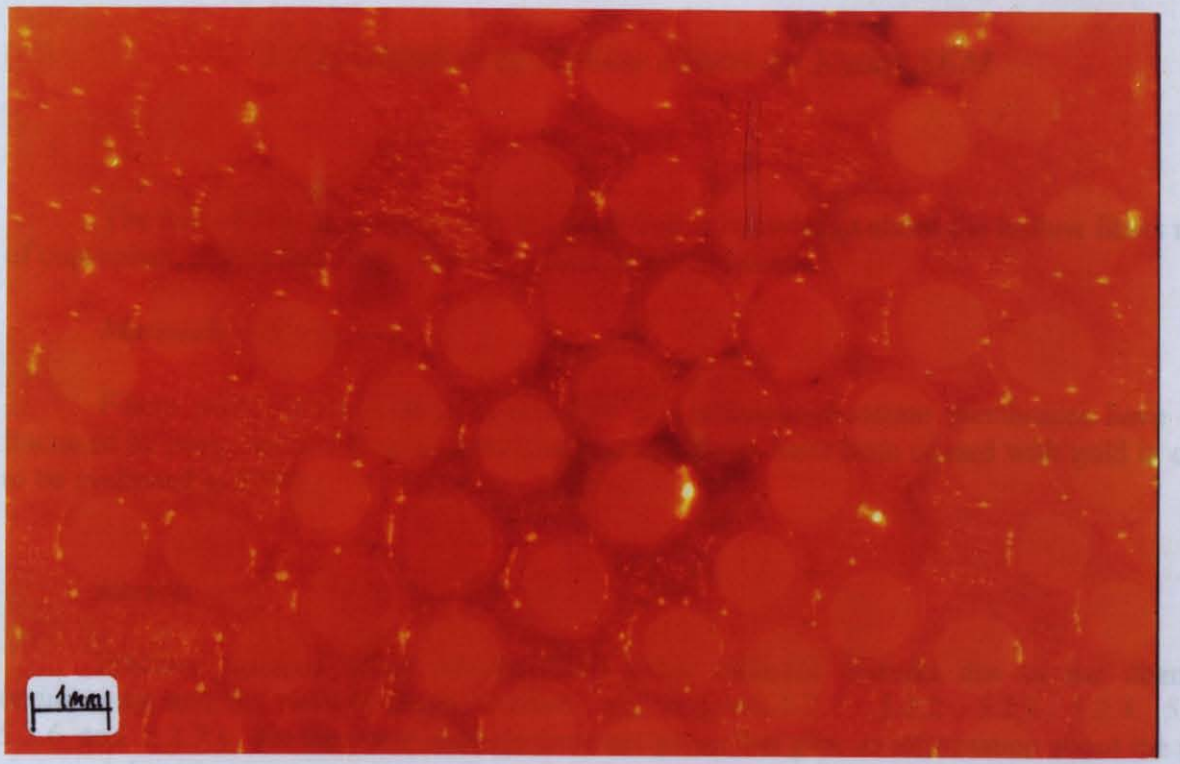

Figure 5.1.4 : Vertical view of a high-flux cellulose-diacetate dialyser fiber bundle.

Figure 5.1.5 : Vertical view of a used cuprophan fiber bundle.

5.2 Evaluation of Hollow Fibers by Using SEM

The aim of this experiment was to obtain better knowledge about the hollow fibers made of cuprophan, polysulfone and cellulose-diacetate membranes.

Materials and methods

Fibers made of cuprophan, polysulfone and cellulose-diacetate membranes have been fractured by using liquid nitrogen. Afterwards , these fibers have been coated with gold in order to be evaluated in SEM.

Results

Fracture surfaces of all hollow fibers show different features due to the chemical composition and the manufacturing methods used (Figures 5.2.1 , 5.2.2 , 5.2.3., 5.2.4., 5.2.5, 5.2.6 and 5.2.7) . On the outer surfaces there are pores that give us information about the pore sizes and densities.

To reveal clear information on the geometry and the geometrical distribution of the pores , more detailed surface studies are necessary. However micrographs taken (Figures.5.2.8 , 5.2.9 and 5.2.10) give information how the pores are distributed. It is necessary to perform more SEM work to have exact conclusion on the pores.

Pores are not important only in mass transfer , but they may also affect the mechanical behavior of the hollow fibers ,which is also an important issue for preventing backfiltration.

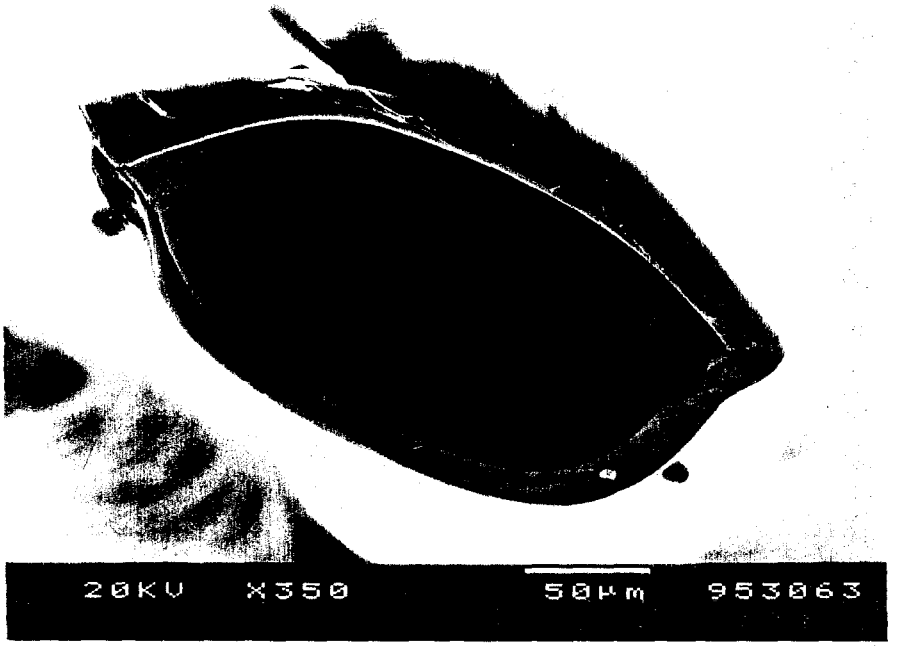

Figure 5.2.1 : Cuprophan hollow fiber cross section.

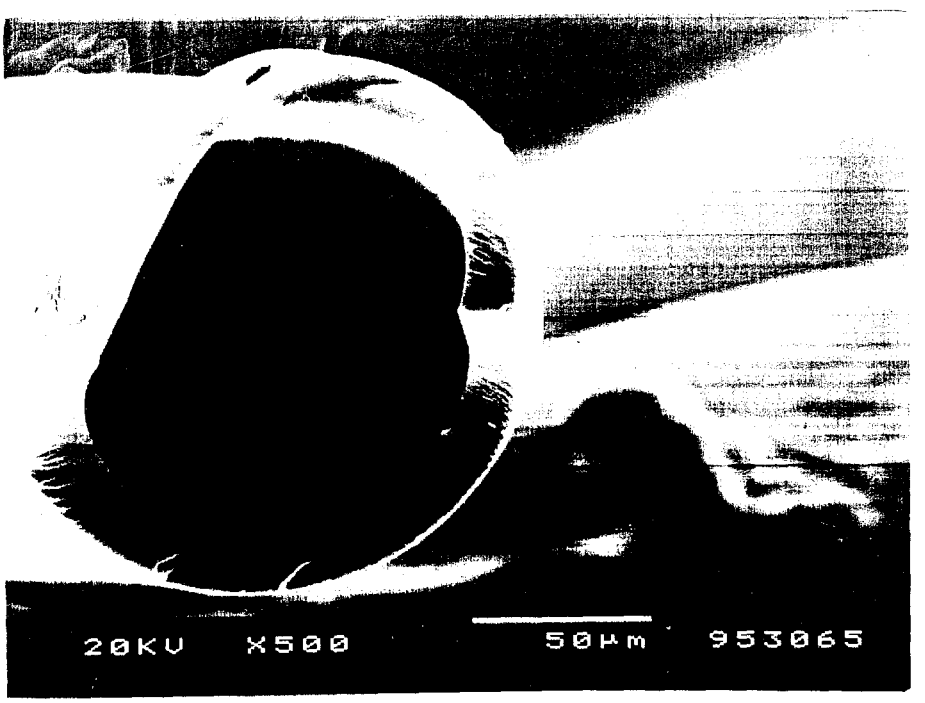

Figure 5.2.2 : Polysulfone hollow fiber cross section.

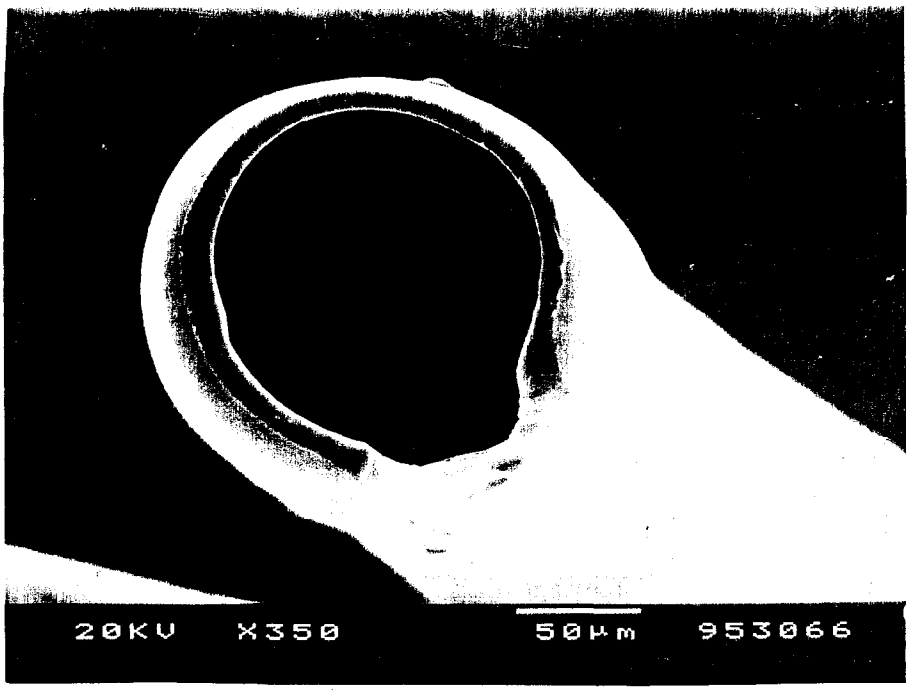

Figure 5.2.3 : Used cuprophan hollow fiber cross section.

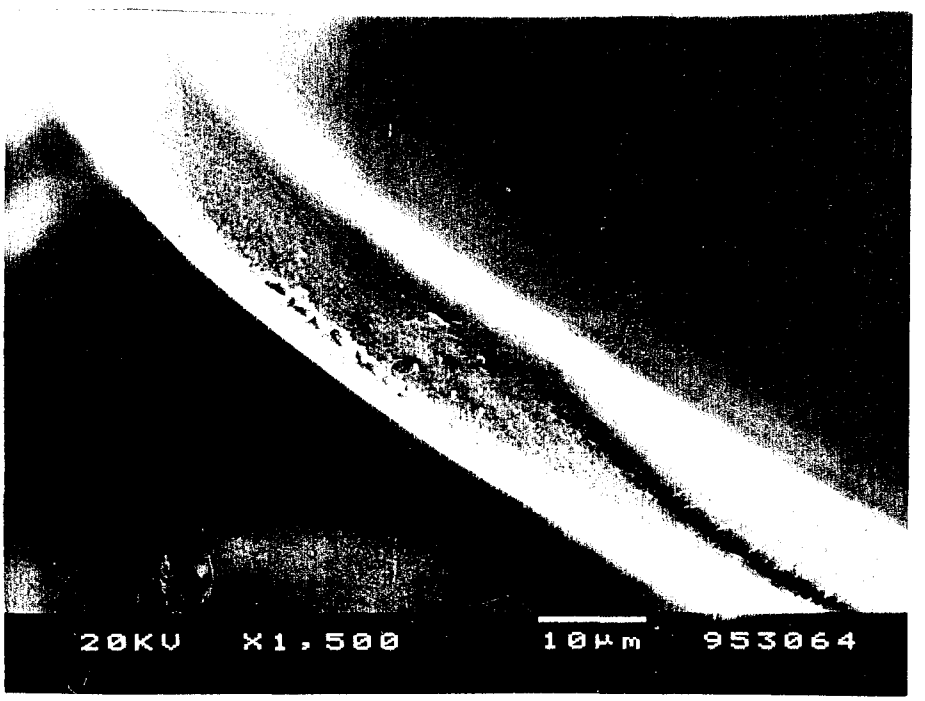

Figure 5.2.4 : Cross-section of the cuprophan membrane wall.

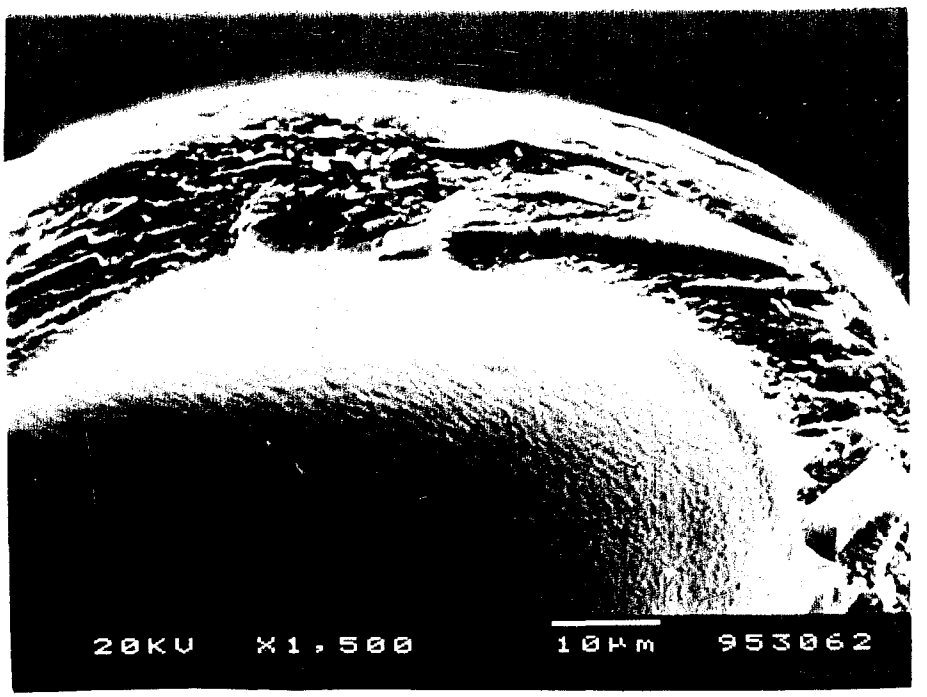

Figure 5.2.5 : Cross-section of the polysulfone membrane wall.

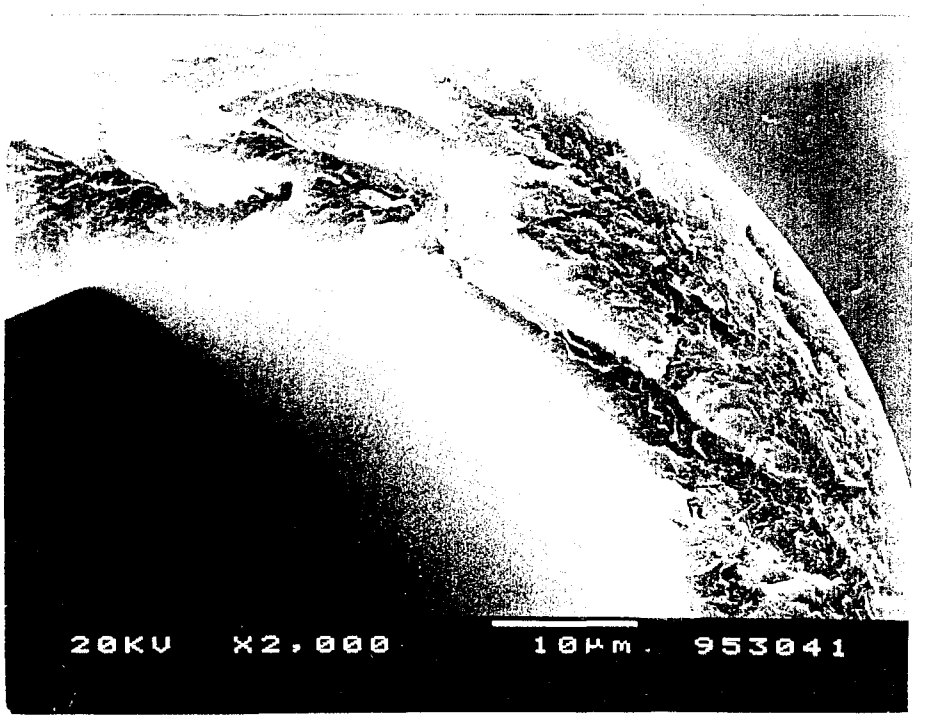

Figure 5.2.6 : Cross-section of the cellulose-diacetate membrane wall.

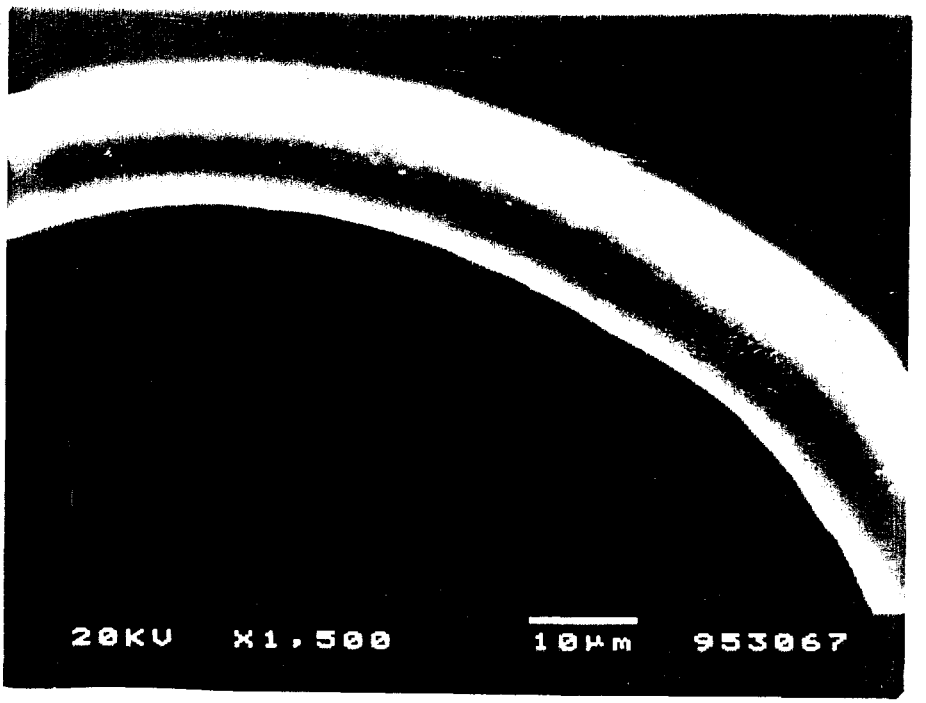

Figure 5.2.7 : Cross-section of a used cuprophan membrane wall.

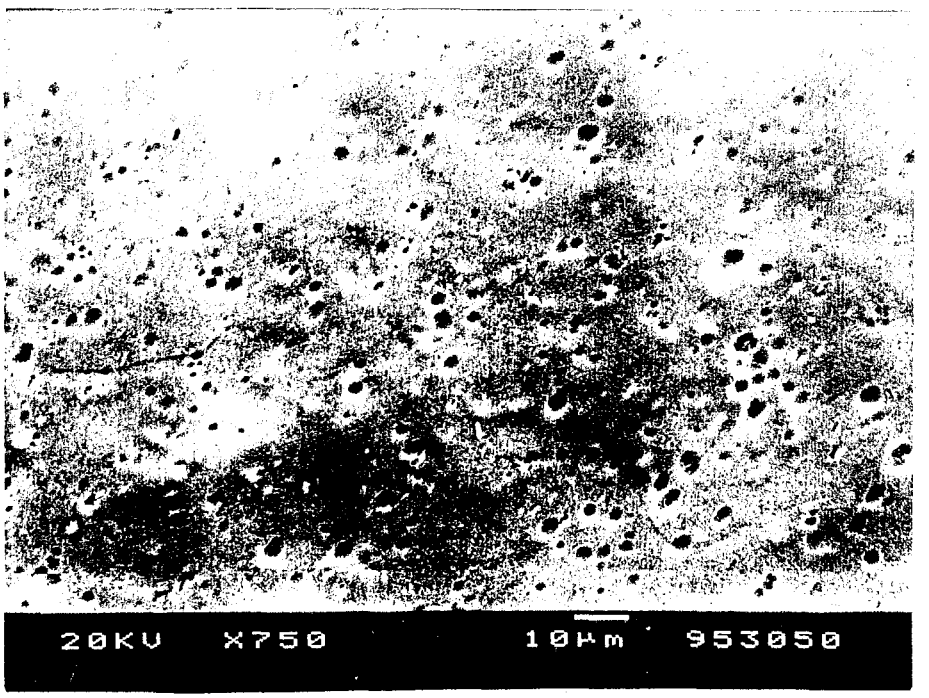

Figure 5.2.8 : Pores on the wall of a cuprophan membrane.

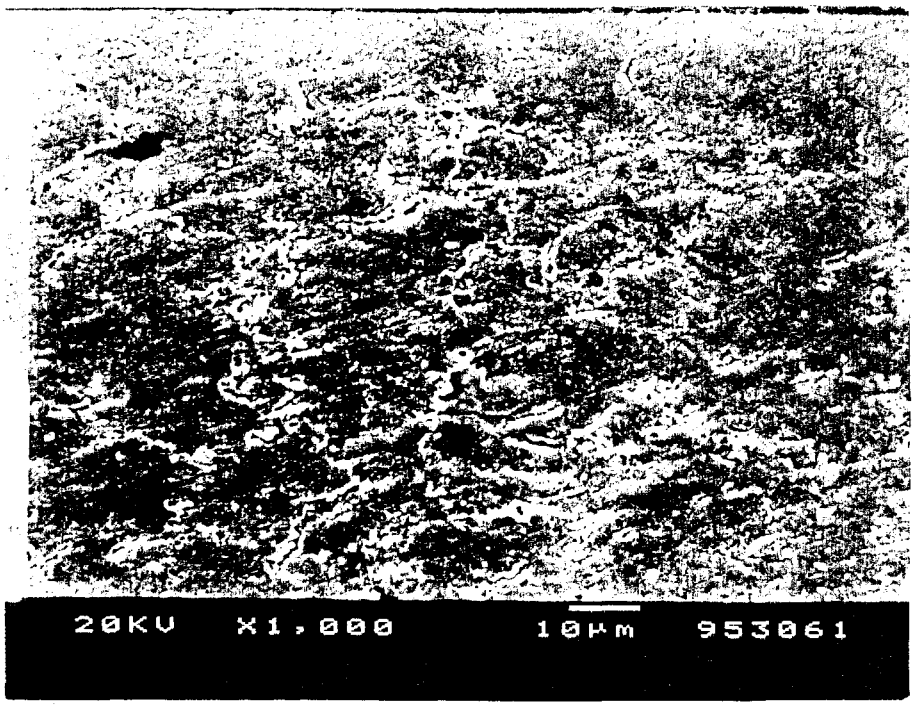

Figure 5.2.9 : Pores on the wall of a polysulfone membrane.

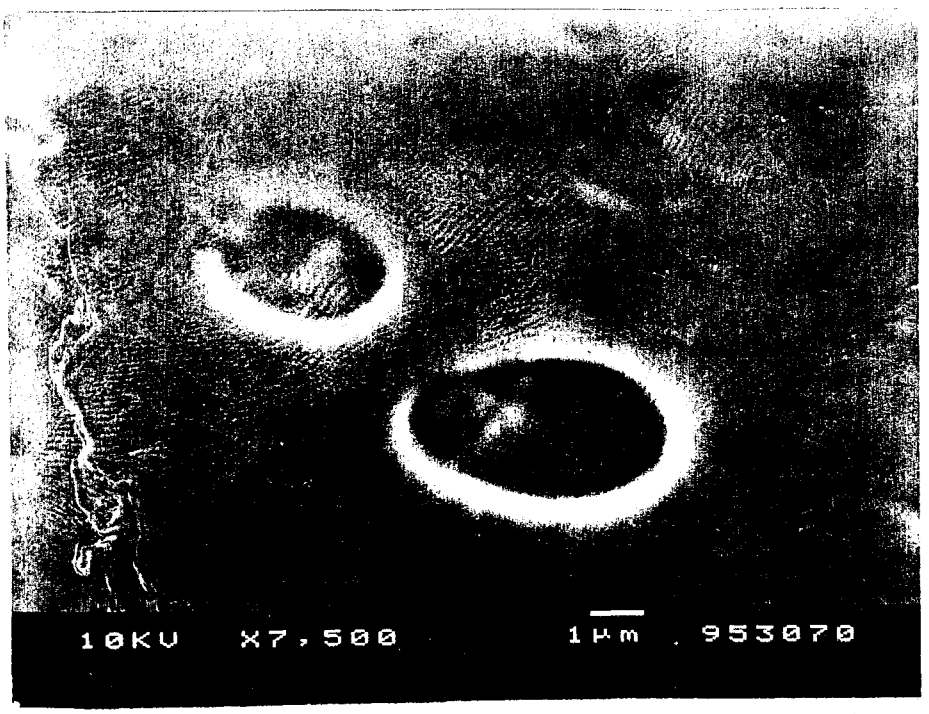

Figure 5.2.10 : Pores on the wall of a cuprophan membrane.

5.3 Tensile Test

The mechanical properties of a dialyser fiber are important during hemodialysis, because there is the risk of a condition called backfiltration . Backfiltration during hemodialysis means that the patient's blood flows to the dialysate compartment or ,vice versa, dialysate flows to the blood compartment (Figure 5.3.1). There is an alarm window in the hemodialysis machine, which stops the machine, when there is a pressure difference between the dialysate and blood compartment more than that of the preset value. This system is not able to detect all the leaks causing serious side effects like infection , hypotension , anemia due to blood losses etc. If the mechanical properties are not good enough , there is always the risk of blood leaks or broken fibers. This means the membranes should be able to stand high physical stresses due to transmembrane pressure (15,18).

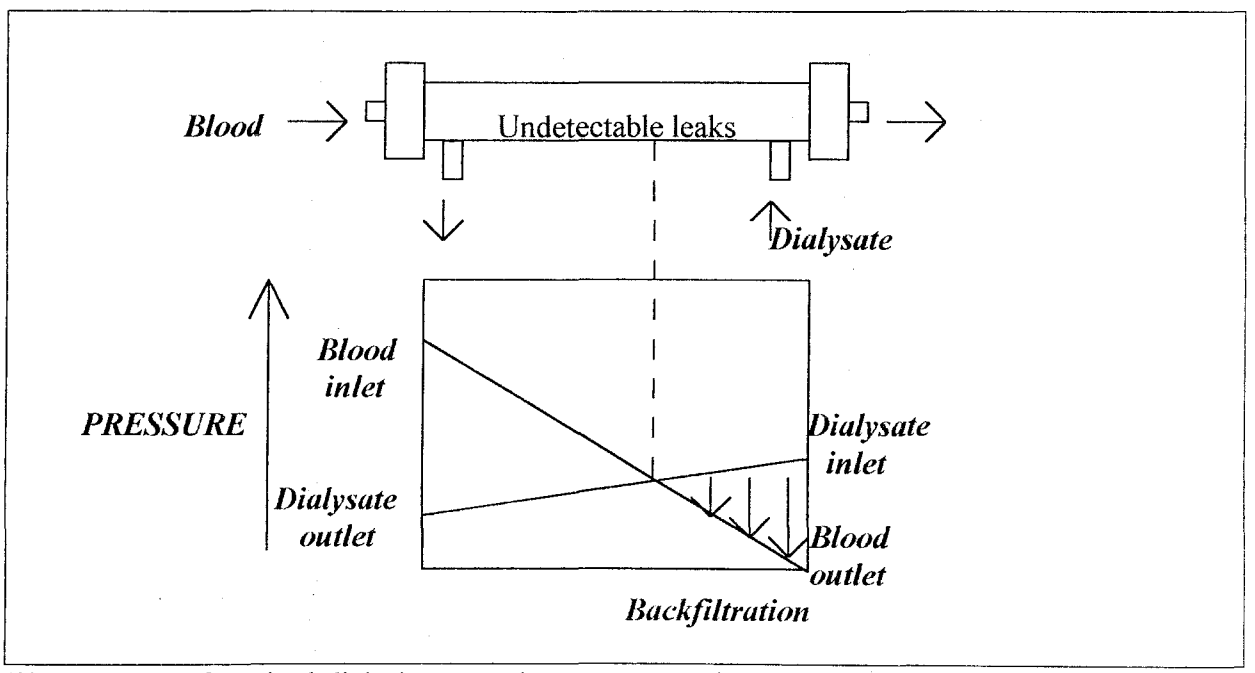

Figure 5.3.1. Standard dialysis procedures may not detect all the leaks and backfiltration can easily occur(18) .

As mentioned before water quality in dialysis centers presents a certain risk for the patient. For example there are standards for the maximum value of bacteria counts and endotoxin concentration in the water after the treatment. Even in developed countries there are still problems with the water treatment(Table 5.3.1).

Table 5.3.1 : The percentage of dialysis centers, in which the bacterial counts and endotoxin concentration are above the accepted standard, in USA and in Germany(20)

Country	Bacteria counts above 200 CFU/ml (CFU : Colony forming unit) %	Endotoxin concentration above 1 ng/ml %
USA	52	5
Germany	40	23

The risk of backfiltration is especially important in centers reusing dialysers. Reusing worsens the tensile strength and the clearance of the dialyser. It was not possible to perform mechanical test on a reused dialyser fiber , because reusing is not performed in Turkey.The possibility , that the reuse technique is less safe than single use , has been considered recently (13).

Materials and Methods

For tensile test, four different dialysers with cuprophan, cellulosediacetate and polysulfone have been cut and opened. 20 fibers from each dialyser have been taken and bundled together for testing.

Results

The data obtained from this experiment.are shown in Table 5.3.2.and in Figure 5.3.2.

Table 5.3.2: Tensile test results.

Membrane	*Wall Thickness of*	*Fiber Diameter (inner)*	*Breaking point*	*Elongation* %
1.Cuprophan (Clirans C10 - Terumo)	10μm	200 μm	100 g / fiber	80
2.Cellulosediacetate (Althin-Ultraflux 140).	30 μm	200 μm	50 g / fiber	30
3.Polysulfone (Fresenius UF 40).	40 μm	200 μm	50 g / fiber	80
4.Used Cuprophan (Renak E)	10μm	200 μm	37.5 g / fiber	10

$$\sigma = \frac{Force}{Area}$$

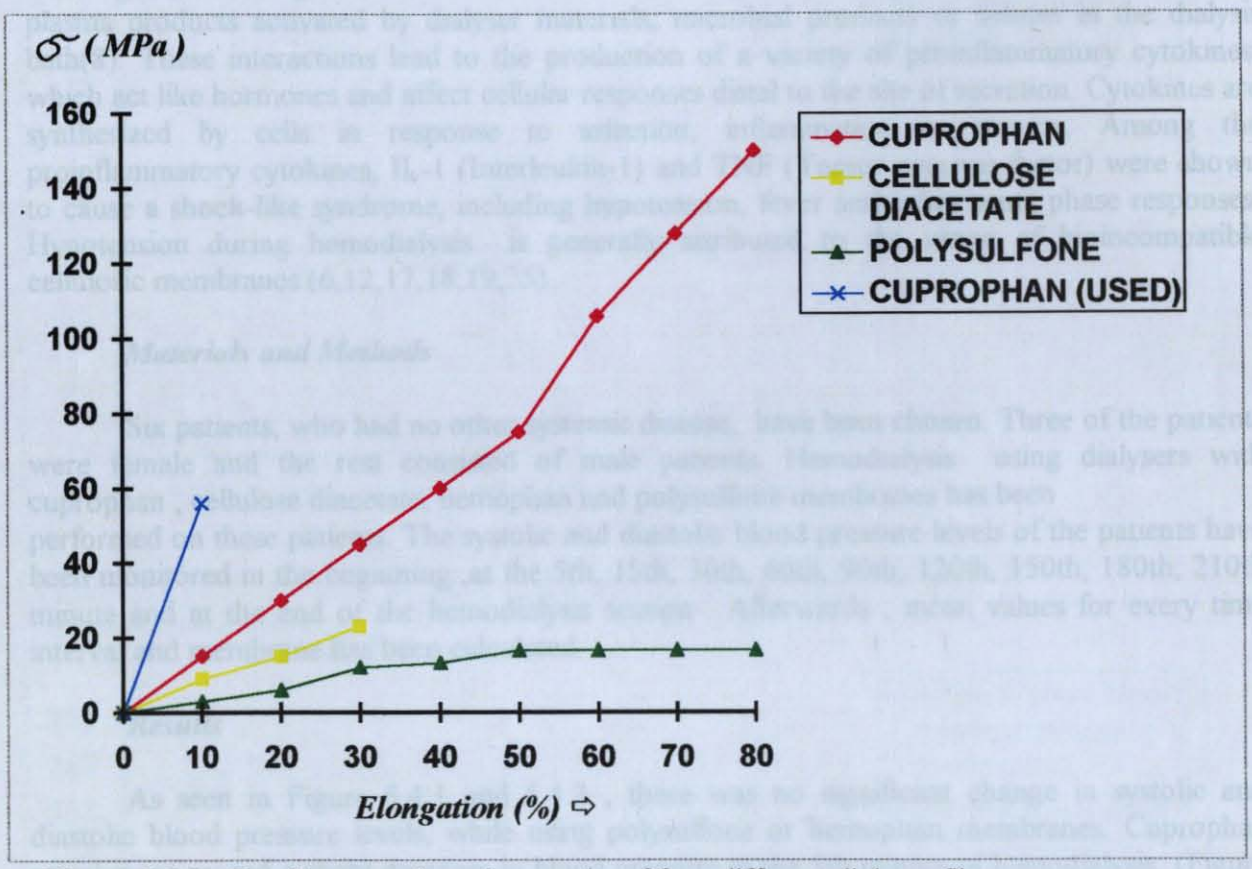

Figure 5.3.2 : Tensile strength testing results of four different dialyser fibers.

5.4 Blood Pressure Changes during Hemodialysis

During hemodialysis human blood leukocytes come into contact with several exogenous challenges , including the surface material of the dialyser membrane., complement and other plasma products activated by dialyser materials, microbial products or solutes in the dialysis bath(8). These interactions lead to the production of a variety of proinflammatory cytokines, which act like hormones and affect cellular responses distal to the site of secretion. Cytokines are synthesized by cells in response to infection, inflammation or trauma. Among the proinflammatory cytokines, IL-1 (Interleukin-1) and TNF (Tumor necrosis factor) were shown to cause a shock-like syndrome, including hypotension, fever and other acute phase responses. Hypotension during hemodialysis is generally attributed to the usage of bioincompatible cellulosic membranes (6,12,17,18,19,25).

Materials and Methods

Six patients, who had no other systemic disease, have been chosen. Three of the patients were female and the rest consisted of male patients. Hemodialysis using dialysers with cuprophan , cellulose diacetate, hemophan and polysulfone membranes has been performed on these patients. The systolic and diastolic blood pressure levels of the patients have been monitored in the beginning ,at the 5th, 15th, 30th, 60th, 90th, 120th, 150th, 180th, 210th minute and at the end of the hemodialysis session . Afterwards , mean values for every time interval and membrane has been calculated.

Results

As seen in Figure 5.4.1 and 5.4.2 , there was no significant change in systolic and diastolic blood pressure levels, while using polysulfone or hemophan membranes. Cuprophan membranes caused a slight decrease in blood pressure at the 5th minute of hemodialysis (Figure 5.4.3). With cellulose diacetate membranes ,blood pressure levels were constant until the 15th minute of the dialysis. Afterwards severe hypotension has been monitored (5.4.4). Even in one patient(16.6%) , hypotension was so severe that the dialysis session had to be terminated.

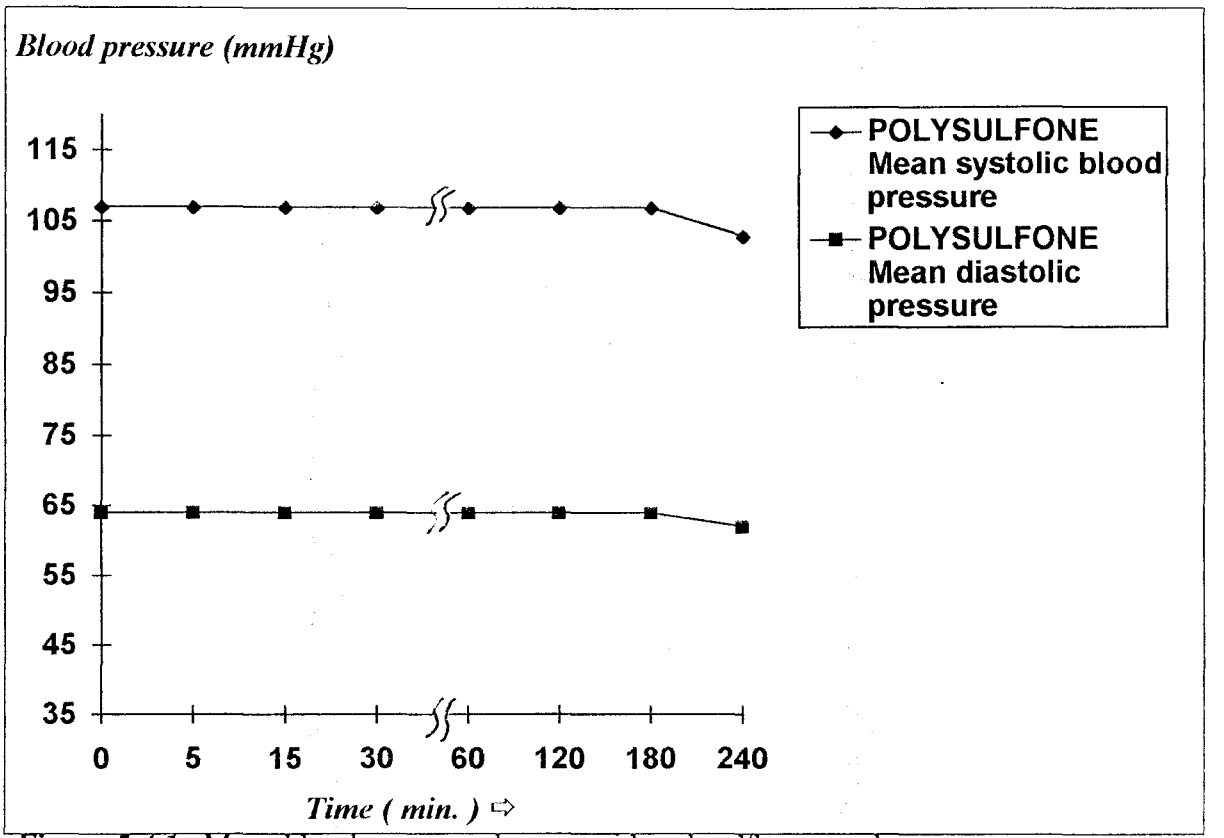

Figure 5.4.1. Mean blood pressure changes with polysulfone membranes.

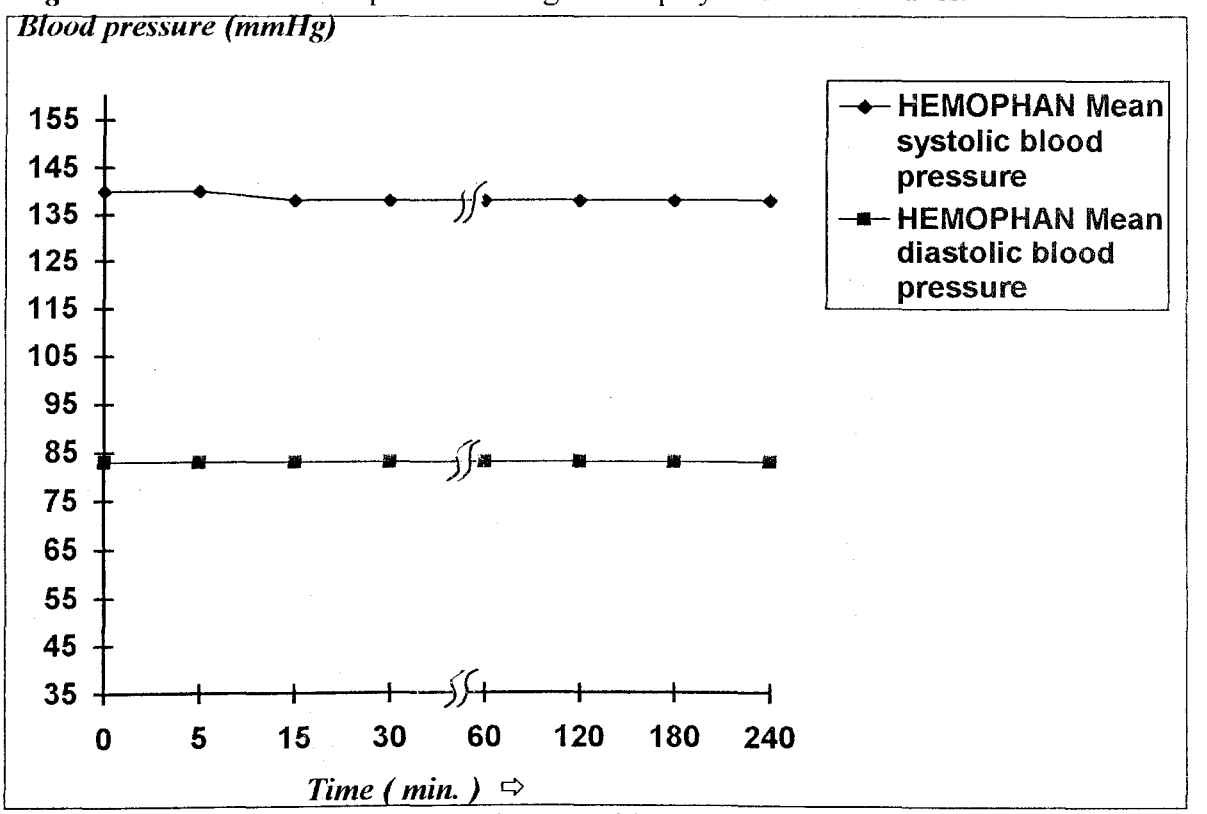

Figure 5.4.2. Mean blood pressure changes with hemophan membranes.

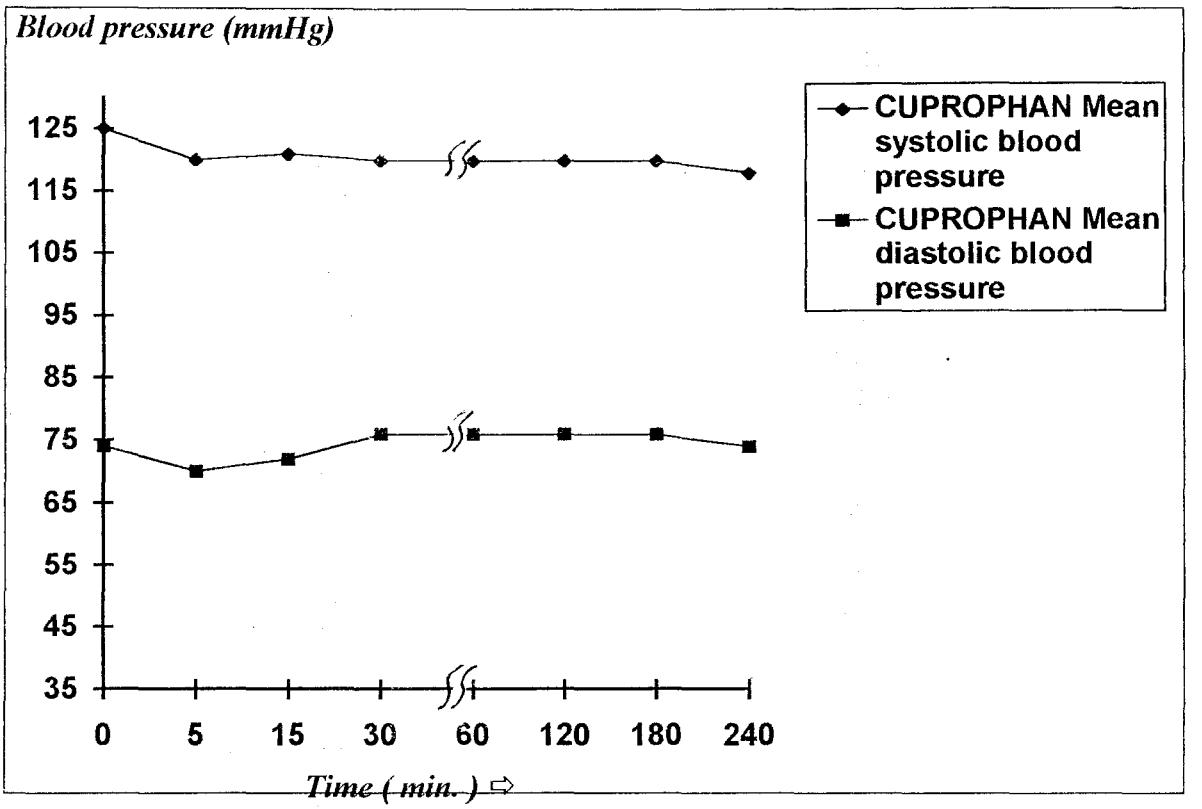

Figure 5.4.3. Mean blood pressure changes with cuprophan membranes.

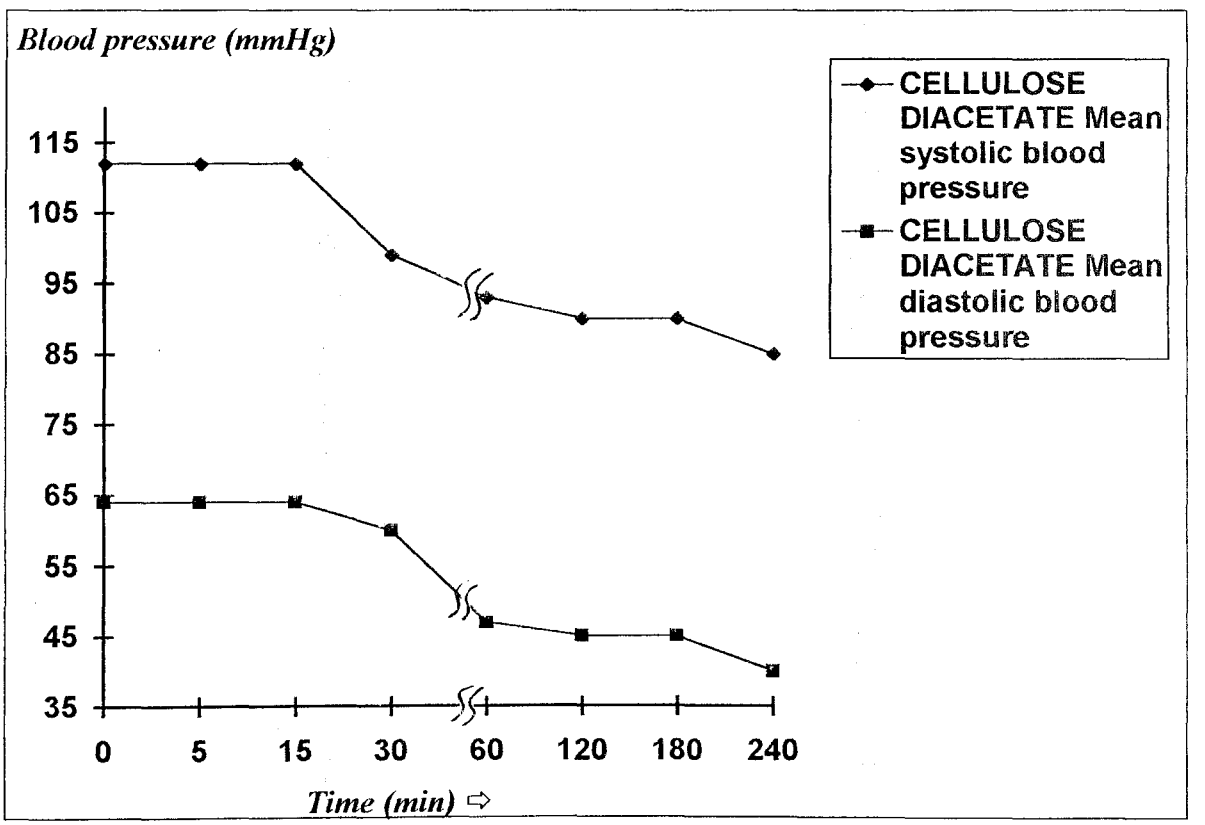

Figure 5.4.4. Mean blood pressure changes with celulose-diacetate membranes.

Table 5.4.1 : Mean diastolic and systolic blood pressure (± Standard Deviation) changes during hemodialysis with polysulfone and hemophan membranes.

Material / *Time(min.)*	Systolic / Diastolic blood pressure *mmHg* *Polysulfone*	Systolic / Diastolic blood pressure *mmHg* *Hemophan*
0	107 ± 30.33 / 64 ± 16.73	140 ± 26.45 / 83 ± 11.54
5	107 ± 30.33 / 64 ± 16.73	140 ± 26.45 / 83 ± 11.54
15	107 ± 30.33 / 64 ± 16.73	140 ± 26.45 / 83 ± 11.54
30	107 ± 30.33 / 64 ± 16.73	140 ± 26.45 / 83 ± 11.54
60	107 ± 32.76 / 64 ± 17.88	140 ± 38.81 / 83 ± 11.54
120	107 ± 32.76 / 64 ± 17.88	140 ± 38.81 / 83 ± 11.54
180	107 ± 32.76 / 64 ± 17.88	140 ± 38.81 / 83 ± 11.54
240	107 ± 32.76 / 64 ± 17.88	140 ± 38.81 / 83 ± 11.54

Table 5.4.2 : Mean diastolic and systolic blood pressure (± Standard Deviation) changes during hemodialysis with cellulose-diacetate and cuprophan membranes.

Material / *Time(min.)*	Systolic / Diastolic blood pressure *mmHg* *Polysulfone*	Systolic / Diastolic blood pressure *mmHg* *Hemophan*
0	112 ± 27.63 / 64 ± 17.81	125 ± 26.45 / 74 ± 14.76
5	112 ± 27.63 / 64 ± 17.81	120 ± 27.36 / 70 ± 19.55
15	112 ± 27.63 / 64 ± 17.81	121 ± 23.49 / 72 ± 10.32
30	112 ± 27.63 / 64 ± 17.81	120 ± 26.45 / 76 ± 11.54
60	99 ± 30.37 / 47 ± 16.73	120 ± 38.81 / 76 ± 11.54
120	93 ± 32.76 / 45 ± 17.88	120 ± 38.81 / 76 ± 11.54
180	90 ± 32.81 / 45 ± 17.88	120 ± 38.81 / 76 ± 11.54
240	85 ± 38.79 / 40 ± 16.43	110 ± 32.51 / 74 ± 15.82

5.5 Transient Leukopenia during Hemodialysis

During dialysis with membranes from unmodified, regenerated cellulose, a transient leukopenia (decrease in white blood cells) is observed. The degree of leukopenia depends on the membranes and the tubings used and is possibly a consequence of complement 5a activation. Due to the fall in oxygen partial pressure, the cells are trapped in the pulmonary microvasculature ,but these cells taken into account return to the circulation after a short residence time in the lung. The hypoxia observed in dialysis appears to be multifactorial as the reduction of the oxygen partial pressure could be avoided by changing the dialysate buffer (9,17,18,19,23,26) .

In conclusion , transient leukopenia is membrane dependent and reversible. A contribution of the leukopenic effect to hypoxemia appears to be caused rather than by the use of a special dialysate buffer by entrapment of the cells in the lungs. The influence of a dialyser membrane on the oxygen partial pressure levels remains a matter of some debate.

Materials and Methods

The blood samples have been taken from the arterial side of the dialysis set at beginning ,at the 5th, 15th, 30th, 60th, 120th, 180th minute and at the end of the hemodialysis session. Afterwards, complete blood count has been performed using Coulter Counter. Mean white blood cell count for every sampling time and dialyser membrane material has been calculated.

Results

As shown in Figure 5.5 and in Table 5.5., the highest reduction in white blood cell count has been observed during the 15th minute of hemodialysis performed with dialysers with cellulose-diacetate membranes and with cuprophan membranes , but leukopenia with cuprophan membranes (18%) was not high compared to cellulose-diacetate (40%) . Reduction in white blood cell count caused by hemophan(12%) and polysulfone membranes(10%) was the lowest at the fifth minute of the dialysis compared to other membranes. .

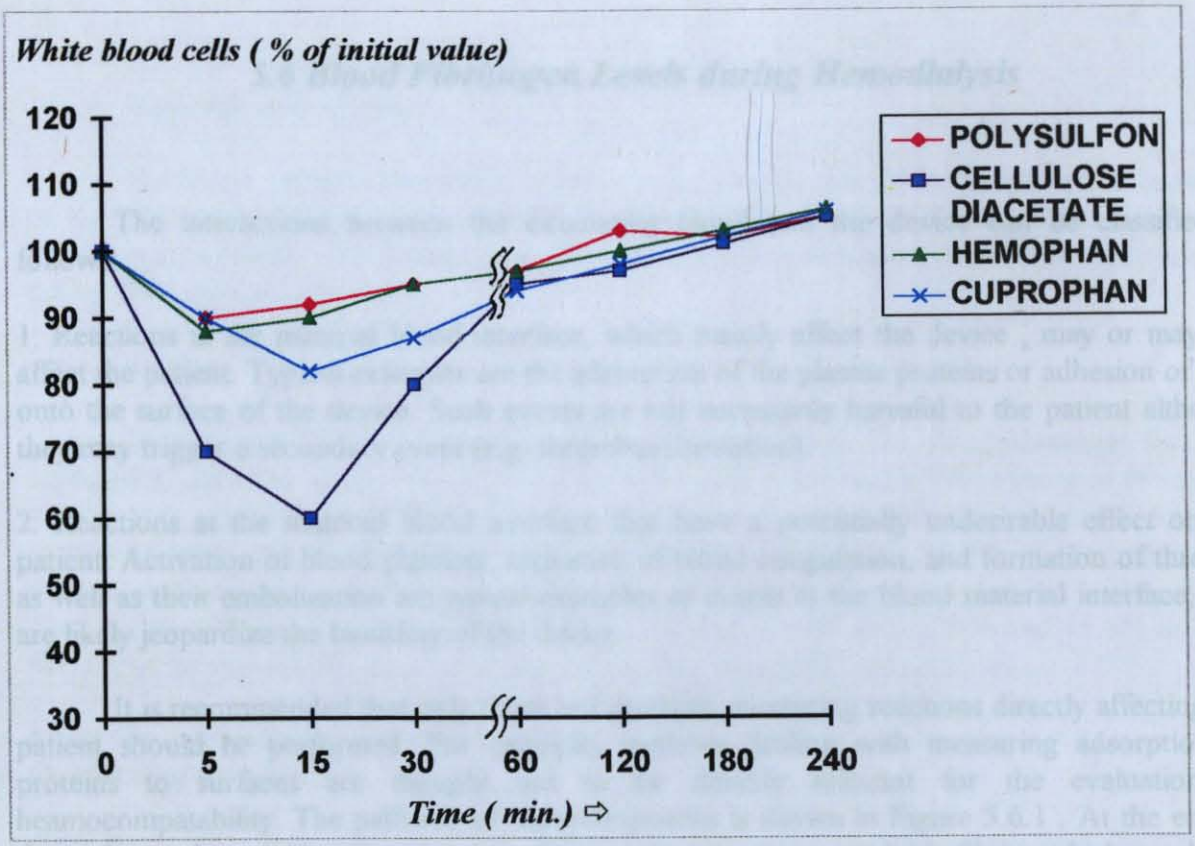

Figure 5.5: Mean white blood cell count during dialysis with polysulfone, hemophan, cellulose diacetate and cuprophan membranes.

Table 5.5 : Mean white blood cell (WBC) count (± Standard Deviation) during hemodialysis with different membranes

Membrane / *Time(min.)*	*Polysulfone*	*Cellulose-diacetate*	*Hemophan*	*Cuprophan*
	WBC/mm³			
O	7760 ± 445	7550 ± 1001	7720 ± 295	7650 ± 287
5	7440 ± 493	6600 ± 1288	7520 ± 296	7550 ± 275
15	7850 ± 529	7600 ± 408	8000 ± 200	7250 ± 184
30	8000 ± 200	8033 ± 130	8180 ± 178	7600 ± 192
60	8140 ± 216	8300 ± 152	8190 ± 122	7750 ± 152
120	8320 ± 330	8400 ± 152	8200 ± 122	7850 ± 152
180	8260 ± 340	8540 ± 843	8200 ± 187	8000 ± 197
240	8250 ± 370	7920 ± 189	8200 ± 187	8100 ± 157

5.6 Blood Fibrinogen Levels during Hemodialysis

The interactions between the circulating blood and the device can be classified as follows:

1. Reactions at the material blood interface, which mainly affect the device , may or may not affect the patient. Typical examples are the adsorption of the plasma proteins or adhesion of cells onto the surface of the device. Such events are not necessarily harmful to the patient although they may trigger a secondary event (e.g. thrombus formation).

2. Reactions at the material blood interface that have a potentially undesirable effect on the patient. Activation of blood platelets, activation of blood coagulation, and formation of thrombi as well as their embolization are typical examples of events at the blood material interface, that are likely jeopardize the biosafety of the device.

It is recommended that only those test methods measuring reactions directly affecting the patient should be performed. For example, methods dealing with measuring adsorption of proteins to surfaces are thought not to be directly relevant for the evaluation of heamocompatability. The pathway of thrombogenesis is shown in Figure 5.6.1 . At the end of the pathway the soluble plasma protein fibrinogen converts to insoluble fibrin, which is a loose mesh of interlacing strands. It is converted by the formation of covalent cross-linkages to a dense, tight aggregate (2,6,10,19).

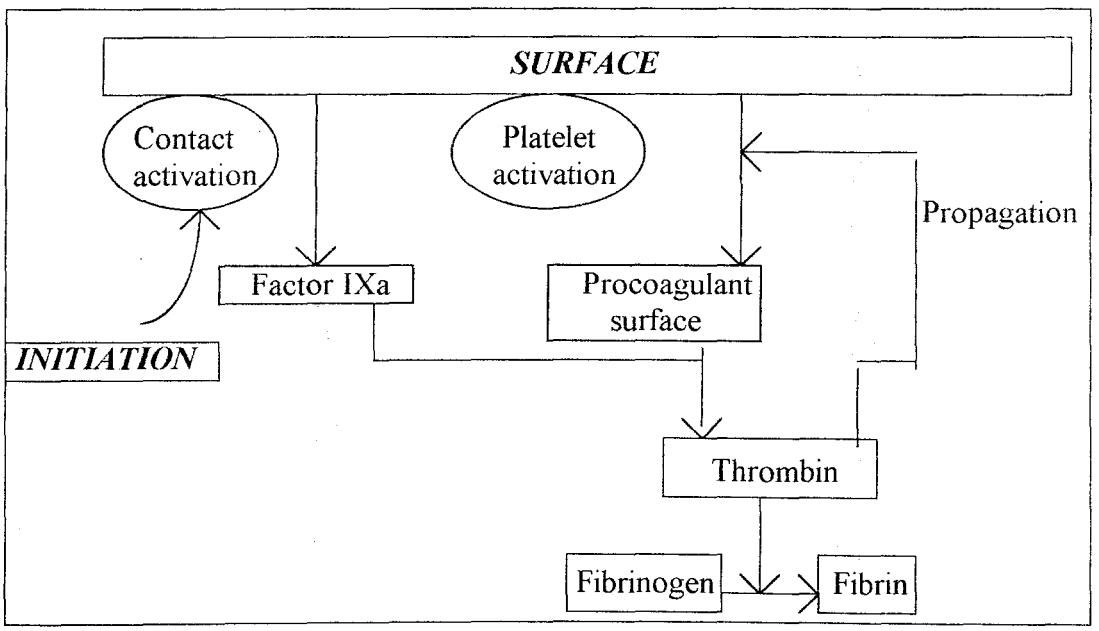

Figure 5.6.1 : Surface induced activation of the coagulation pathway (2).

Materials and Methods

The blood samples have been taken from the arterial side of the dialysis set at beginning ,at the 30th, 60th, 120th, 180th and at the end of the hemodialysis session. After determining the fibrinogen levels , the mean blood level values have calculated for certain time intervals during the hemodialysis session.

Results

As mentioned before , if there is a trend for coagulation, the blood fibrinogen levels are expected to decrease. A decrease to 77.23% of the initial value at the 30th minute of the dialysis session and a decrease to 77.23% of the initial value at the end of the dialysis session has been monitored when using cellulose-diacetate dialysers(Figure 5.6.2). In 16.6% of the patients, the dialysis session had be terminated because of clot formation in the dialyser with cellulose diacetate membranes. In other dialysers a minor decrease between 19.73% and 15.6% in blood fibrinogen levels has been monitored and no clot formation has been detected.

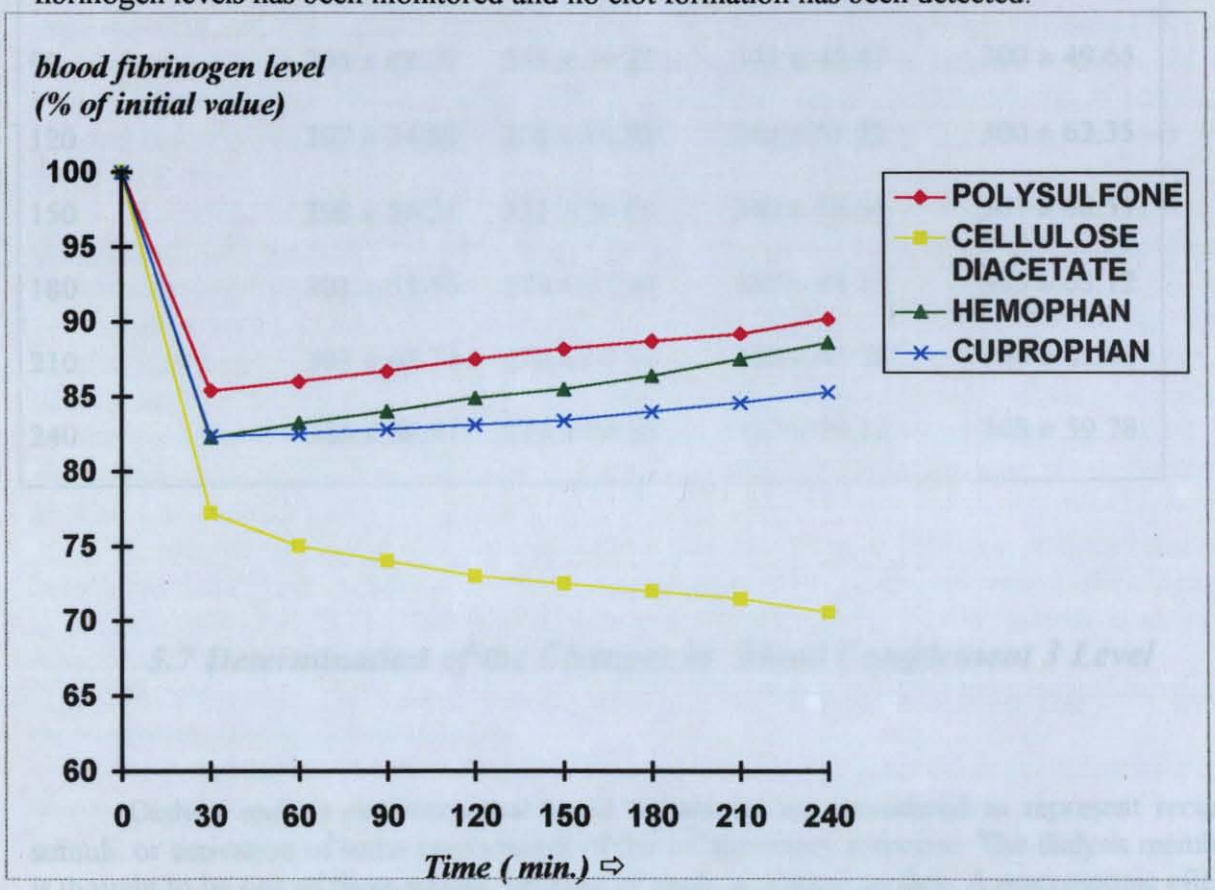

Figure 5.6.2: Mean blood fibrinogen levels during hemodialysis using different membranes .

Table 5.6 : Blood fibrinogen levels (± Standard Deviation) during hemodialysis with different membranes.

Membrane / *Time(min.)*	*Polysulfone*	*Hemophan*	*Cellulose-diacetate*	*Cuprophan*
	%mg			
0	340 ± 76.21	316 ± 77.43	470 ± 42.15	362 ± 65.32
30	290 ± 55.72	259 ± 72.32	363 ± 30.32	298 ± 63.24
60	292 ± 65.34	262 ± 64.43	352 ± 38.17	299 ± 58.91
90	294 ± 44.77	265 ± 59.21	347 ± 43.47	300 ± 49.65
120	297 ± 34.89	268 ± 49.58	343 ± 51.12	300 ± 62.35
150	298 ± 54.21	272 ± 38.61	340 ± 56.61	301 ± 68.51
180	301 ± 55.56	273 ± 72.34	338 ± 43.35	303 ± 63.12
210	303 ± 62.74	276 ± 68.17	336 ± 42.28	306 ± 61.11
240	306 ± 58.61	279 ± 74.56	332 ± 79.32	308 ± 59.78

5.7 Determination of the Changes in Blood Complement 3 Level

Dialysis and its extracorporeal blood circulation are considered to represent recurrent stimuli or activation of some components of the inflammatory response. The dialysis membrane is thought to be one of these stimuli, because of unphysiological surface. A macroscopic effect of such an inflammatory stimulus should cause a rise in body temperature. A rise of about 0.5 C is generally observed during dialysis (25).

The complement system is part of the immune system and represents an unspecified defense mechanism of the body. It consists of 20 proteins, which can be stimulated by bacteria

and endotoxins , but also by membrane materials. Specific surface properties, which are not yet understood, lead to its cascade-like activation, where proteins enzymatically split to active fragments , e.g. C3 to C3a , the latter also .being called as "anaphylotoxins".

Complement activation is considered the number, one parameter, to characterize biocompatability of dialysis membranes today. The interest in complement in hemodialysis originated from the observation of dialysis-induced leukopenia (2.,9,11,17,18,19).

Because of their potent biological activities of these anaphylotoxins and the frequently large magnitude increase observed during hemodialysis , plasma C3a and C5a have been extensively used as an index of biocompatability. The decision to develop and use new membranes mainly follows their reduced capacity to induce complement activation in clinical dialysis and animal studies.

In contrast to the activation of the complement cascade by bacteria , which follows classical pathway, most hemodialysis membranes activate complement primarily via the alternative pathway(Figure 5.7.1). Activation is initiated with the deposition of C3b on the membrane surface. C3b, with the help of factor B forms the C3 and C5 convertases . These enzymes are able to cleave the anaphylotoxins C3a from C3 and C5a from C5 molecules in an autocatalytic process. Cleavage of C5 by C5-convertase results in generation of two split products C5a and C5b with C5b being part of the terminal complement complex (TCC) or membrane -attack complex (MAC) . The TCC is a complex molecule that is composed from C5b to C9 molecules. Once assembled , MAC is inserted into the cell membrane of a biological cell and forms a porous structure. The destruction if the cell membrane's integrity leads to cell death (17).

A series of hypotheses have been advanced to explain, why membranes lead to complement activation. Activation of the alternate pathway by other biological surfaces appears to be initiated by following covalent binding of C3b to the surface hydroxyl-groups.

Since regenerated cellulose (Cuprophan) has an abundance of free hydroxyl-groups on its glucosan rings , one may postulate, that these hydroxyl-groups provide potential covalent binding sites for activated C3, thereby favoring C3 activation. In contrast, cellulose acetate and hemophan have a portion of their hydroxyl-groups substituted by either acetyl or DEAE (di-ehtyl-amino-ethyl) residues. One may therefore postulate that these residues block the binding sites of C3 , thus limiting C3 activation.

Cheung et al . found that cuprophan does not bind more to C3a than cellulose acetate or hemophan does. Instead, after exposure to serum cuprophan membranes bound more factor B , a protein, that promotes complement activation, than factor H , a protein that inhibits complement activation (17).

Rateberg et al. demonstrated a considerable absorption of the regulatory protein factor H on hemophan membranes (17,24,26).

In conclusion dialysis membranes stimulate complement activation to different extents. The mechanism of the stimulation obviously depends on membrane interactions with inhibitory proteins rather than the availability of free-hydroxyl-groups.

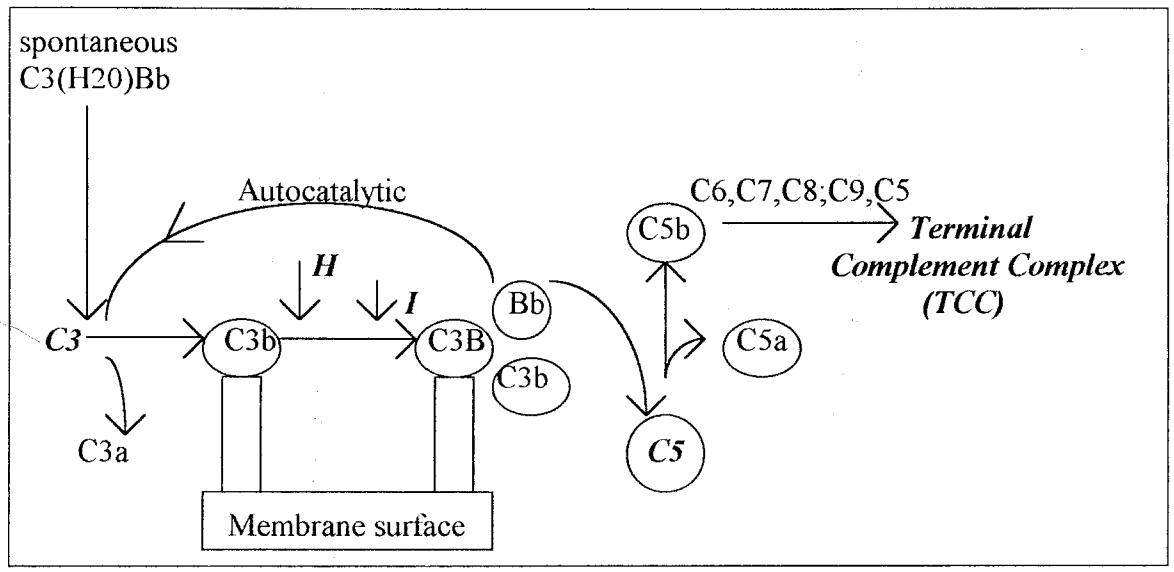

Figure 5.7.1 : Complement activation (Alternative pathway) (18)

Materials and Methods

Six patients, who had no other systemic disease, have been chosen. 3 of the patients were female and the rest were of male patients. Hemodialysis using dialysers with cuprophan , cellulose diacetate, hemophan and polysulfone membranes has been performed on the patients. The blood samples have been taken from the arterial side of the dialysis set at beginning ,at the 5th,15th minute and at the end of the hemodialysis session. Afterwards , blood C3 levels were determined by using RID (Radial immune diffusion) assay.

Results

In Figure 5.7.2, it can be seen that polysulfone membrane causes the minimum rise in blood C3 levels. The values determined by using hemophan membranes are close to the values of polysulfone membranes.Cuprophan has the highest capacity to induce complement activation followed by cellulosediacetate membranes.

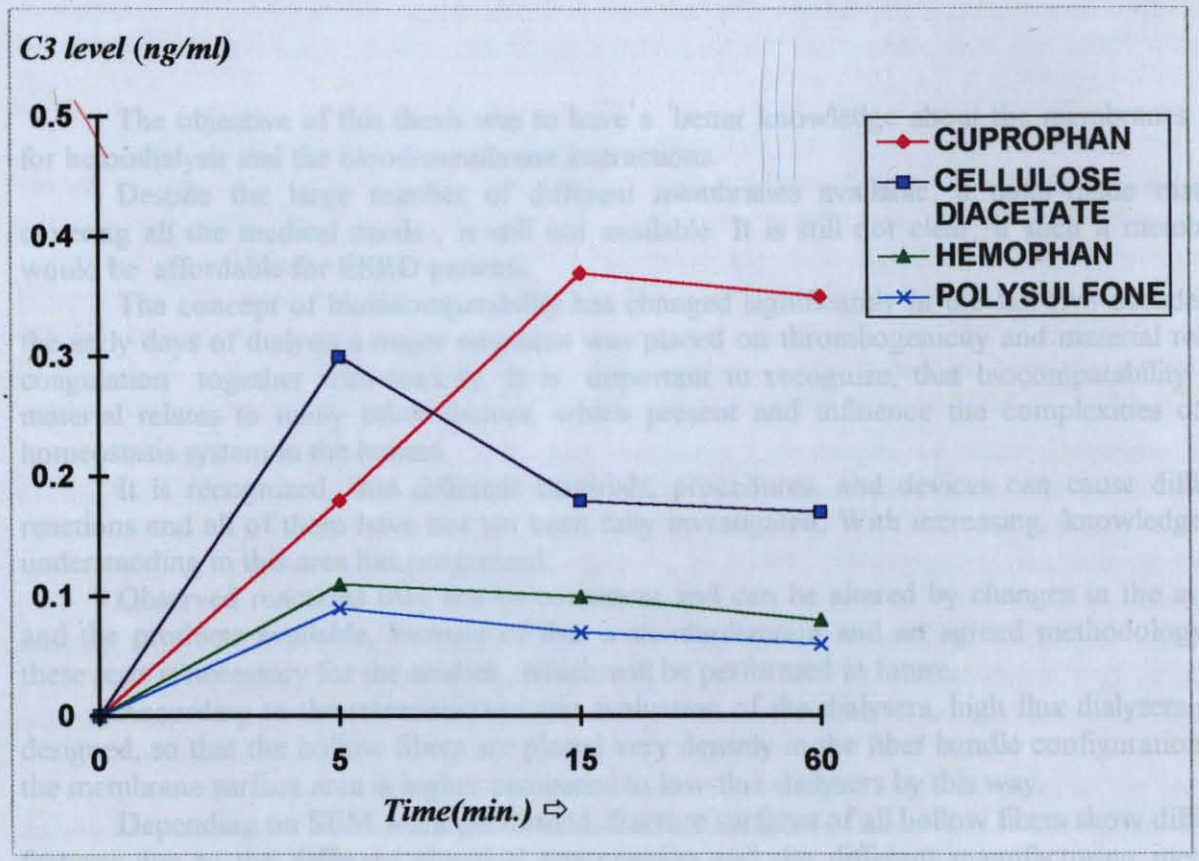

Figure 5.7.2. Blood C3 levels using dialysers with different membranes.

Table 5.7 : Blood C3 levels (± Standard Deviation) during hemodialysis with different membranes.

	Type of Membrane			
	Polysulfone	***Hemophan***	***Cellulose-diacetate***	***Cuprophan***
Time (min.)	***ng/ml***	***ng/ml***	***ng/ml***	***ng/ml***
0	0	0	0	0
5	0.09 ± 0.002	0.11 ± 0.02	0.30 ± 0.05	1.18 ± .0.2
15	0.07 ± 0.001	0.10 ± 0.15	0.18 ± 0.03	0.37 ± 0.6
60	0.06 ± 0.001	0.08 ± 0.18	0.17 ± 0.03	0.35 ± 0.5

6. CONCLUSION

The objective of this thesis was to have a better knowledge about the membranes used for hemodialysis and the blood-membrane interactions.

Despite the large number of different membranes available, a tailor-made material covering all the medical needs , is still not available. It is still not clear, if such a membrane would be affordable for ESRD patients.

The concept of bioincompatability has changed significantly in the last two decades. In the early days of dialysis a major emphasis was placed on thrombogenicity and material related coagulation together with toxicity. It is important to recognize, that biocompatability of a material relates to many other factors, which present and influence the complexities of the homeostasis system in the human.

It is recognized, that different materials, procedures, and devices can cause different reactions and all of them have not yet been fully investigated. With increasing knowledge our understanding in this area has progressed.

Observed reactions may not be consistent and can be altered by changes in the system and the products available, because of that a standardization and an agreed methodology of these tests is necessary for the studies , which will be performed in future.

According to the stereomicroscopic evaluation of the dialysers, high flux dialysers were designed, so that the hollow fibers are placed very densely in the fiber bundle configuration and the membrane surface area is higher compared to low-flux dialysers by this way.

Depending on SEM work performed, fracture surfaces of all hollow fibers show different features due to the different chemical composition and the different manufacturing methods used. On the outer surfaces there are pores, that give us information about the pore sizes and densities. To reveal clear information on the geometry and the geometrical distribution of the pores , more detailed surface studies are necessary. It is necessary to perform more SEM work to have exact conclusion on the pores. Pores are not important only in mass transfer , but they may also affect on the mechanical behavior of the hollow fibers ,which is also an important issue for preventing backfiltration. Thus , the results of mechanical testing include geometrical effect of the pores together with material chemistry and physics. Both affecting parameters have to be distinguished.

Tensile test showed that cuprophan could stand the highest stress, but the value mentioned of cuprophan is reduced up to 1/3 of its initial level after being served for one session during hemodialysis so that changes in properties present a certain risk of backfiltration , if these membranes are reused. On the other hand cellulose-diacetate and polysulfone membranes had similar breaking points during the test.

No significant change in systolic and diastolic blood pressure levels has been monitored while using polysulfone or hemophan membranes. Cuprophan membranes caused a slight decrease in blood pressure at the 5th minute of hemodialysis . With cellulose diacetate membranes ,blood pressure levels were constant until the 15th minute of the dialysis. Afterwards severe hypotension has been monitored with cellulose-diacetate membranes leading to the termination of dialysis in 16.6% of the patients. The systolic blood pressure levels decreased by 14% at the end of the first hour and by 21% at the end of the hemodialysis performed with

cellulose-diacetate membranes. The diastolic blood pressure dropped by 23% at the end of the first hour and by 36% at the end of the dialysis with cellulose-diacetate membranes. Depending on these data, cellulose-diacetate membranes cause hypotension more than the other dialysers do.

The highest reduction in white blood cell count has been observed during the 15th minute of hemodialysis performed with dialysers with cellulose-diacetate membranes , and with cuprophan membranes, but leukopenia with cuprophan membranes (18%) was not so high compared to cellulose-diacetate (40%) . Reduction in white blood cell count caused by hemophan(12%) and polysulfone membranes(10%) was the lowest at the fifth minute of the dialysis compared to other membranes. It has been detected, that the leukopenia during hemodialysis was reversible as mentioned in the literature and cellulose-diacetate membranes caused the highest reduction in the white blood cell count of the patients (9,17,18,19,23,26) .

After the laboratory tests performed to reveal the changes of blood fibrinogen levels during hemodialysis, a decrease to 77.23% of the initial value at the 30th minute of the dialysis session and a decrease to 77.23% of the initial value at the end of the dialysis session have been monitored, when using cellulose-diacetate dialysers. In 16.6% of the patients, the dialysis session had be terminated because of clot formation in the dialyser with cellulose diacetate membranes. In other dialysers a minor decrease between 19.73% and 15.6% in blood fibrinogen levels has been monitored and no clot formation has been detected. It can be concluded that cellulose-diacetate membranes have the highest tendency for causing coagulation in the dialyser compared to other membranes(2,6,10,19).

Depending on the blood tests to detect the changes in the blood C3 level of the patients during hemodialysis it has been found out that polysulfone membranes cause the minimum rise in blood C3 levels(0.09 ng/ml at the fifth minute of the dialysis). The values determined by using hemophan membranes are close to the values of polysulfone membranes(0.11 ng/ml at the fifth minute of the dialysis). Cuprophan has the highest capacity to induce complement activation(0.37 ng/ml at the fifteenth minute of the dialysis) followed by cellulosediacetate membranes (0.3 ng/ml at the fifth minute of the dialysis). Depending on these data polysulfone membranes caused the minimum increase in the blood C3 level , which has a great influence on the inflammatory response .discussed in the biocompatability issue(17,24,26).

It has been concluded, that polysulfone membranes have the best biocompatability, while cellulosediacetate membranes had the worst ones. It is necessary to perform these tests on more patients and add more membrane types to the study like, PMMA(Polymethylmethacrylate) , PAN (Polyacrylonitrile) , EVAL (Ethylvinylalcohol copolymer) membranes . As mentioned before , more SEM work is also necessary to find out the pore sizes, pore distribution , and surface conditions of different membranes..

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