1. Historical overview

Membrane and dialyser development has always closely followed trends in dialysis therapy and advances in scientific cognition (**figure 1.1**). Therefore, the choice of membrane polymer, the membrane form and its physical and biological properties have changed over time, having to adapt to various clinical demands. Following a period of basic research in the field of dialysis, which started as early as 1861, one can identify three major phases in which fundamental scientific discoveries in renal replacement therapy particularly influenced membrane and dialyser development. In phase I, 1945-1965, the major concern was simply to sustain life and to make treatment available for a larger group of patients (**table 1.1**). Dialysers were more or less "hand-made", being manufactured only in small quantities. Removal of uraemic toxins was mainly achieved by diffusion and limited to low molecular weight substances. Phase II (1966-1985) was characterised by increasing patient numbers and the availability and widespread application of industrially manufactured, disposable dialysers. Scientists and physicians turned their attention to device compatibility and treatment tolerance parameters. In the beginning, mainly only acute side effects were considered, but later parameters of the body's humoral and cellular defence systems, which could not always be directly linked to patient reactions, also received much attention. Furthermore, removal of middle molecules came to be considered important, so that the contribution of convection to toxin removal was increased by developing membranes that were more open. Phase III (1986 to the present) can be considered a phase of quality considerations. Dialyser and membrane development became directed towards improving survival and quality of life for the patients. The ultimate aim is a symptom-free treatment that should result, in the long-term, in a reduction of morbidity and mortality in chronic haemodialysis patients.

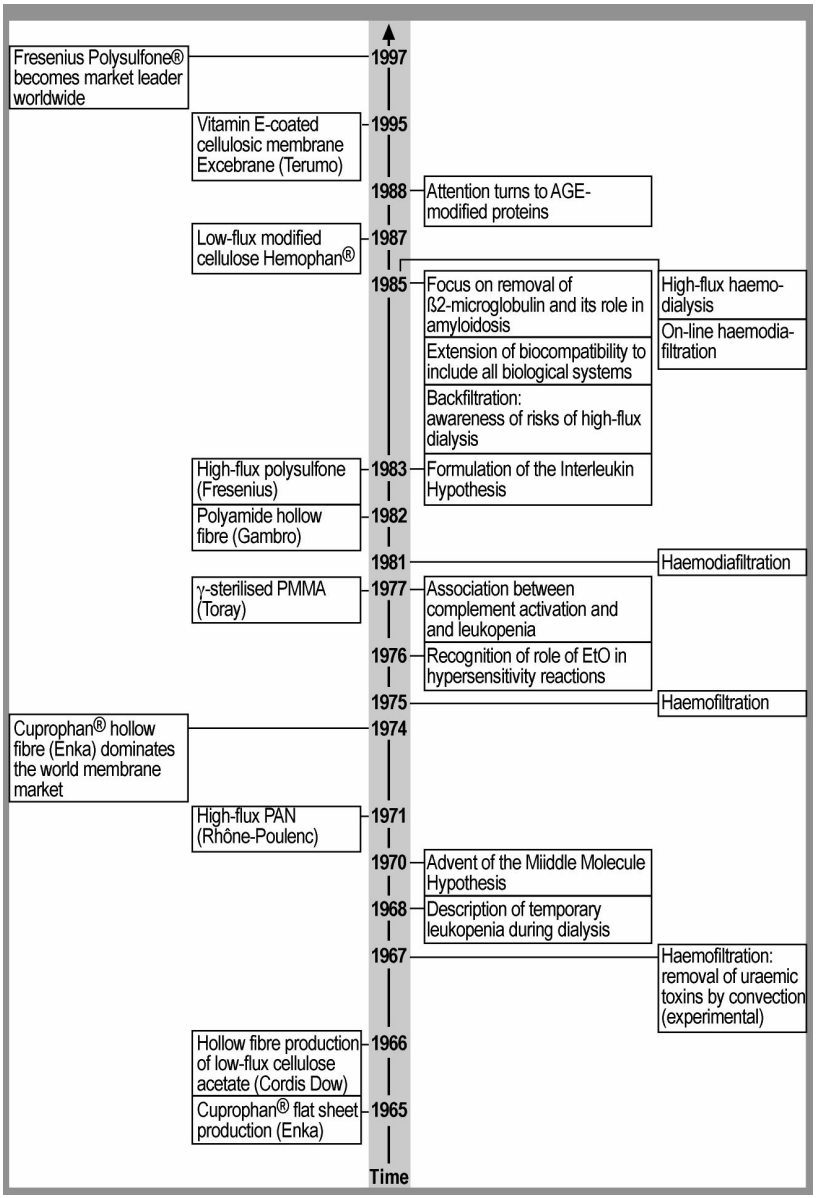

Figure 1.1: Scientific discoveries and key steps in the development of membranes and dialysers.

Phase I: Establishment of haemodialysis as a standard therapy – development of affordable cellulosic membranes and disposable dialysers of adequate performance (1945-1965)

In 1913, Abel and Rountree produced the first "dialysis membrane" from collodium, a cellulose nitrate derivative (**figure 1.2**) [2], and dialysis membranes were made exclusively from cellulose until 1970 (**table 1.1**). During this time, dialysis therapy evolved into a standard treatment and, parallel to this, industrial manufacturing of large quantities of dialysis membranes became possible. These developments included improvements in the geometry of the membrane: a process which went from tubes (dialyser in **figure 1.3** and **1.4**) to coils (dialyser in **figure 1.5** and **1.6**), to flat sheets (**figure 1.7**) and, finally, to hollow fibres (**figure 1.8**). Hollow fibres can be manufactured at high velocities and with a high degree of reproducibility. Advances in production technology permitted a reduction in filter dimensions and blood compartment volume, and allowed the application of higher transmembrane pressures (compare figures **1.6** and **1.8**). In hollow-fibre dialysers, flow conditions are significantly more uniform for blood and dialysis fluid, reducing performance loss due to fluid stagnation. The pioneers in membrane and dialyser development are listed in **table 1.1,** together with their respective landmark inventions that established haemodialysis treatment as a standard therapy.

As in most other technologies, the apparatus used for the treatment has become less elaborate (smaller in size, easier to handle). Particularly the size of dialysers and filters has decreased considerably over time; in fact, this development is still ongoing. A comparison of dialysers from 1970 with present dialysers of equal performance illustrates this point. Miniaturisation can only be accomplished by increasing the performance characteristics of the dialyser or haemofilter and the membrane. With cellulosic membranes, this goal was achieved by reducing the diffusive barrier, i.e. the wall thickness. The strong physical strength of cellulosic membranes, based on their unique chemical structure, allowed considerable wall thickness reductions over time.

Year	Inventor, company	Device, membrane polymer	Development
1861	T. Graham (Glasgow and London, GB)	Vegetable pergament (parchment paper)	Diffusion of cristalloids, not colloids, between separated aqueous solutions: dialysis [1]
1913	J. Abel, L. Rowntree, B. Turner (Baltimore, USA)	*Vivi-diffusion apparatus:* device with cellulose trinitrate (collodion) tubes (figure 1.2)	First artificial kidney used on nephrectomised dogs [2]
1924	G. Haas (Giessen, FRG)	Tubular device Cellulose trinitrate (collodion) (figure 1.3)	First human dialysis [3]
1932	R. Weingand (Bornlitz, FRG)	Tubes from cellulose solutions	First continuous cellulose tube manufacturing [4]
1937	W. Thalheimer (New York, USA)	Cellulose-hydrate (cellophane) (normally used as protective film in the sausage industry)	First flat haemodialysis membrane produced [5]
1944	W. Kolff, H. Berk (Kampen, NL)	*Rotating drum:* stainless steal drum, wound by a cellophane tube (sausage casing) and immersed in a dialysis fluid bath (figure 1.4)	First recovery of an acute renal failure patient [6]
1947	N. Alwall (Lund, S)	*Alwall kidney:* stainless steal drum, wound by membrane coils and immersed in a dialysis fluid bath (figure 1.5)	Ultrafiltration using hydrostatic pressure [7, 8]
1956	W. Kolff, B. Watschinger (Cleveland, USA)	*Coil dialyser:* tubular membrane, sandwiched between woven fibreglass and wrapped around a solid core (figure 1.6)	First employed in the late sixties with a single-pass dialysis fluid delivery system [9]

Year	Inventor, company	Device, membrane polymer	Development
	Travenol (USA)	Twin Coil dialyser: twin blood pathways	First disposable haemodialyser
1960	F. Kiil (Oslo, N)	Kiil dialyser: plate dialyser which could be reassembled; contained grooved polypropylene boards which supported the cellulosic flat sheet membrane (sausage packaging industry) (figure 1.7)	Parallel-flow artificial kidney which could be used without a blood pump [10]
1966	R. Stewart et al. Cordis Dow (USA)	Cellulose acetate hollow fibre** (used for desalination) (figure 1.8)	First capillary hollow-fibre production [11]
1966	Enka AG* (Wuppertal, FRG)	Cuprophan® (regenerated cellulose) flat sheets	First standardised industrial production of flat sheet membranes
1967	L.W. Bluemle, L.W. Henderson (USA)	Polyelectrolyte membrane "Diaflo" (figure 1.9)	First investigations with haemofiltration [12]
1969	Enka AG* (Wuppertal, FRG)	Cuprophan® capillary fibres	
1969	Hospal (Meyzien, F)	AN69® polyacrylonitrile (figure 1.10)	First synthetic membrane with an ultrafiltration coefficient suitable for high-flux dialysis [13]
1970	Gambro (Lund, S)	*Alwall dialyser:* multiple stacked membrane layers separated by thinner membrane support plates (figure 1.11)	First disposable parallel-plate dialyser, presterilised [14]

**Enka later became Akzo Faser, then Akzo Nobel and is now Membrana*
***Functionally regenerated cellulose rather than cellulose acetate because of a de-esterification step in the manufacturing process [15]*

Table 1.1: Pioneers in dialyser and membrane development and their inventions during the evolution of haemodialysis to a standard therapy.

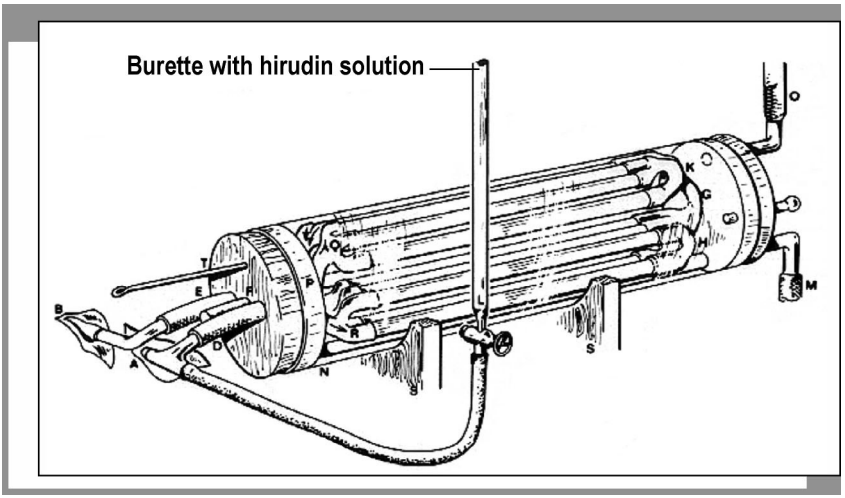

Figure 1.2: Vivi-diffusion apparatus from Abel and Rountree, which was used for dialysis on nephrectomised dogs in 1913.

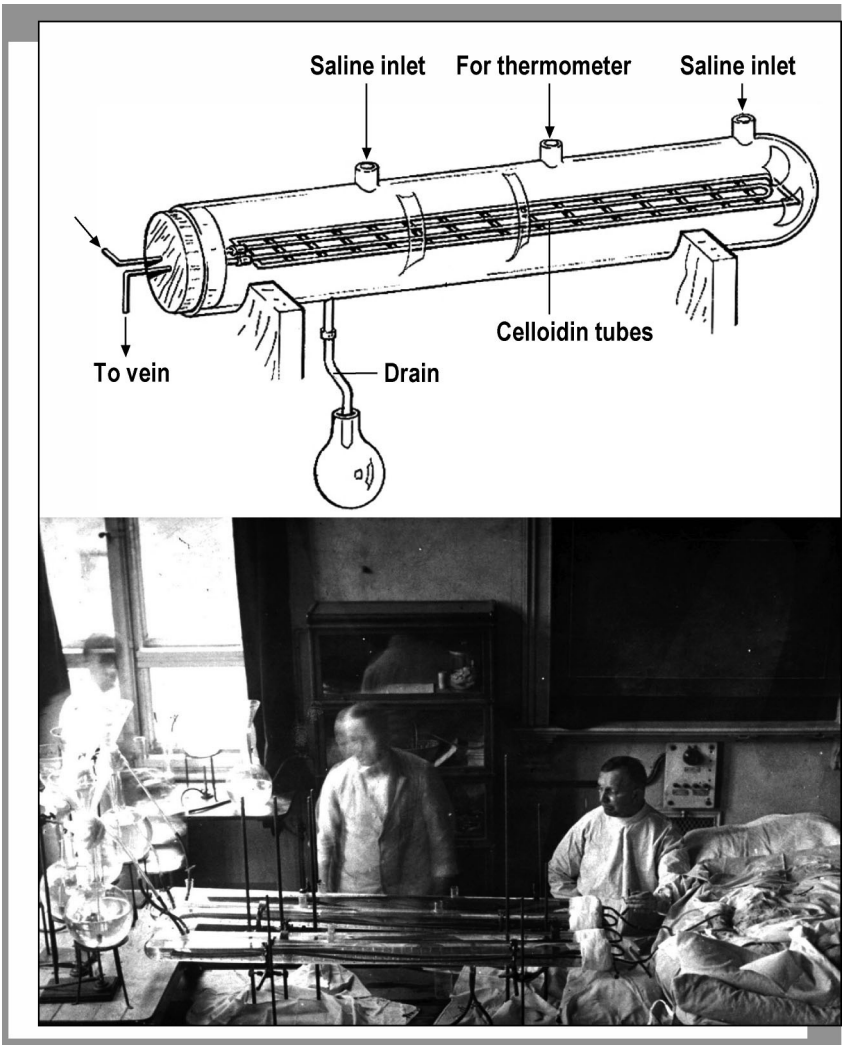

Figure 1.3: Schematic drawing of the "Haas dialyser" and photograph of one of the first human dialysis in 1924.

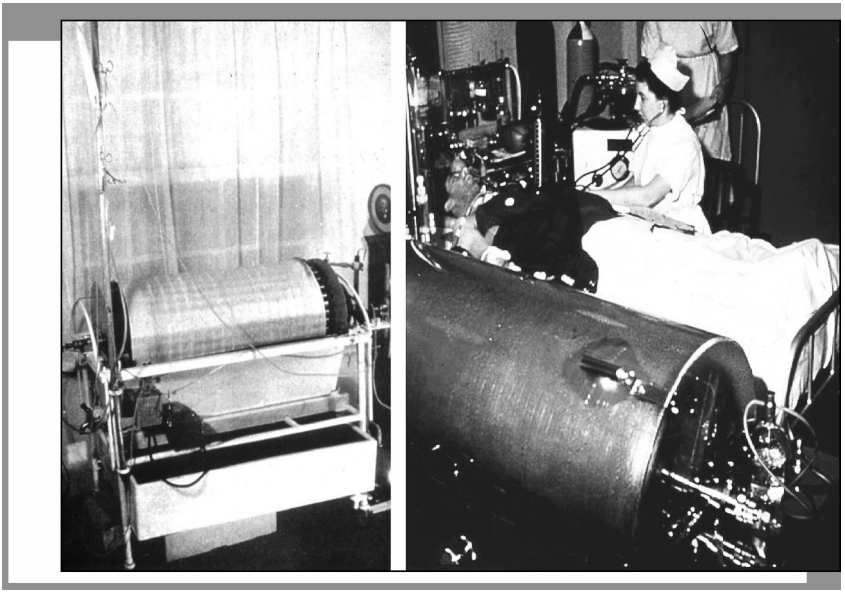

Figure 1.4: Kolff's rotating drum in 1944 (on the left) and dialysis with this device in Glasgow in 1965 (on the right).

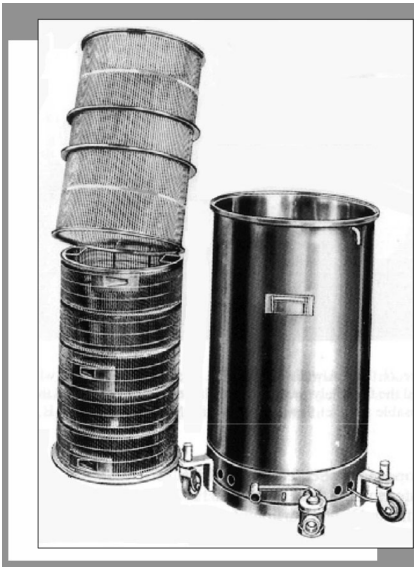

Figure 1.5: Alwall kidney, consisting of a stainless steel drum, wound by membrane coils and immersed in a dialysis fluid bath (1947).

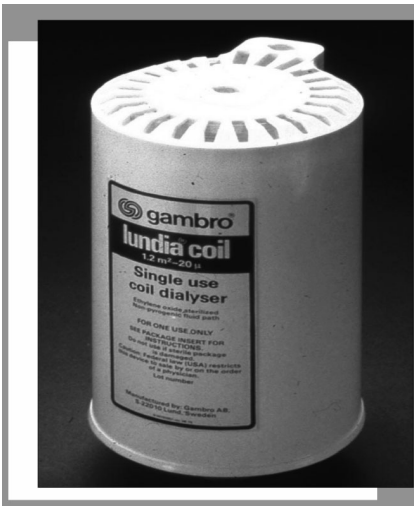

Figure 1.6: Coil dialyser, Lundia 1.2 m², from 1956.

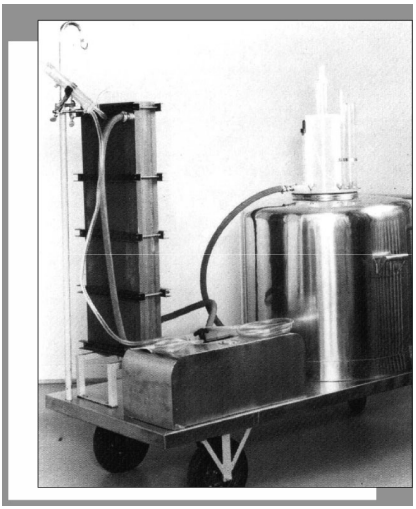

Figure 1.7: Kiil Dialyser from 1960, which could be used without a blood pump.

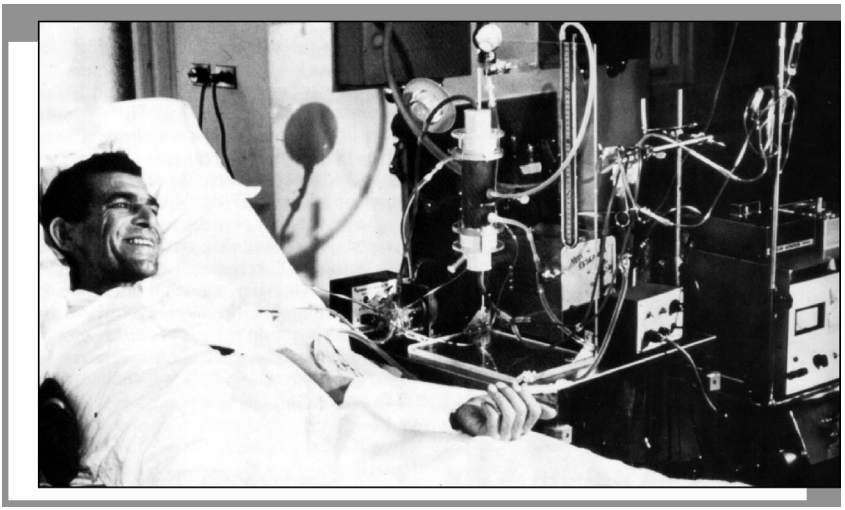

Figure 1.8: Capillary hollow-fibre dialyser from Stewart, CDAK 1.3 (1966).

Phase II: The middle molecule hypothesis, start of the debate on biocompatibility – development of synthetic membranes with greater permeabilities and higher degrees of biocompatibility (1966- 1985)

All early dialysis membranes were of low hydraulic permeability and removed only low molecular weight molecules. Elimination of small uraemic toxins was accomplished predominantly by diffusion. Convection was only employed to remove the interdialytic fluid gain. This concept changed when Bluemle and Henderson published their first results on haemofiltration using a highly permeable "polyelectrolyte" membrane (sodium polystyrene sulfonate and polyvinylbenzyltrimethyl ammonium chlorid, called "Diaflo") in 1967 [12] (**figure 1.9**). The aim of their experiments was to relate the rate of solute removal to the applied pressure gradient (which could be adjusted to the particular clinical situation) and not, as it is the case in diffusion, to the concentration gradient [12]. Although their Diaflo membrane failed to become a successful product commercially, the results initiated a change in direction in membrane development towards the production of membranes with higher permeabilities for larger solutes. The theoretical basis for the use of such highly permeable membranes was supplied in the beginning of the nineteen seventies by the so-called "Middle Molecule Hypothesis": the retention of higher molecular weight uraemic toxins (here molecular weight > 300 up to 2000) was believed to be responsible for a number of clinical manifestations of the uraemic status, and their removal was clearly desirable [16]. The first commercial membrane of high hydraulic permeability was developed in 1969 and introduced into the market in 1971; it was made from an acrylonitrile sodium methallylsulfonate copolymer, better known under the brand name AN69® (Rhône-Poulonc, France) [13] (**figure 1.10**). With this polymer, a new class of dialysis membranes was born: the synthetic membranes. Use of such membranes with increased ultrafiltration properties demanded the development of appropriate dialysis machines with automatic ultrafiltration control, a fact that probably hindered the widespread usage of high-flux dialysis in the years that followed.

Parallel to the introduction of high-flux dialysis, haemofiltration was gaining popularity for some special patient groups. In 1974, the first chronic renal failure patient was treated by haemofiltration [17]. Although widespread application of haemofiltration and also haemodiafiltration [18] is hindered by the greater costs involved compared to standard haemodialysis, the number of patients treated with these methods is still growing, albeit slowly. Almost all dialyser manufacturers have developed a filter containing a synthetic mem-

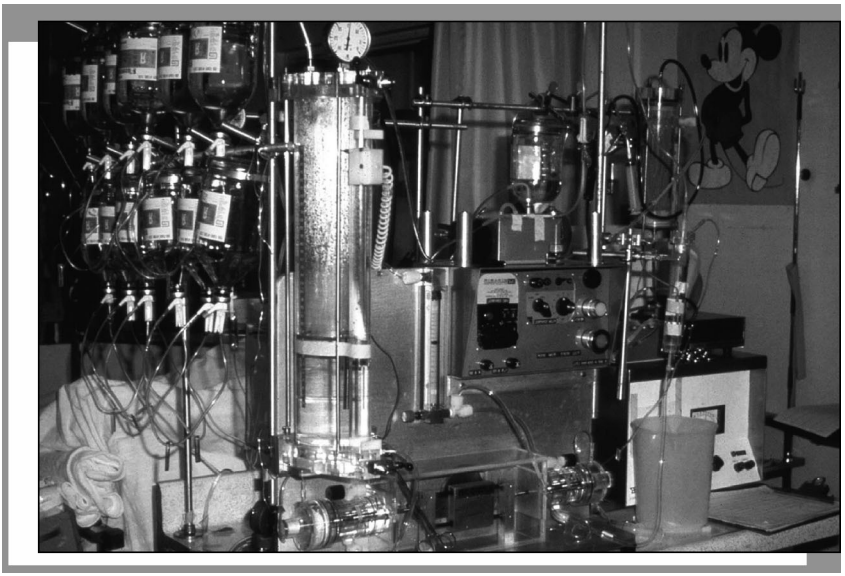

Figure 1.9: Early haemofiltration set-up by Hendersen et al. (approx. 1970).

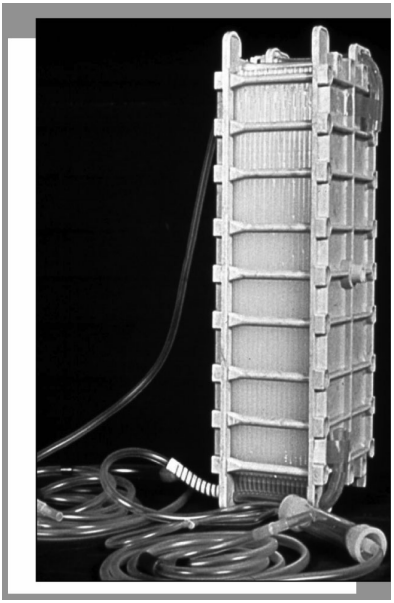

Figure 1.10: First high-flux dialyser from Rhône Poulenc, RP6 with the AN69® membrane (1969).

Figure 1.11: Nils Alwall with the "Alwall dialyser" from 1970 and a modern plate dialyser that was commercially available until the early nineties.

brane of sufficiently high hydraulic permeability for these particular applications.

The development of other synthetic membranes, such as polymethylmethacrylate (PMMA in 1977 by Toray, Japan), polyamide (in 1982 by Gambro, Sweden) and polysulfone (in 1983 by Fresenius, Germany), started in the late seventies and is still ongoing. This development process was further stimulated by the findings that synthetic membranes are generally better accepted by the patient's defence systems than membranes made of regenerated cellulose (e.g. Cuprophan®). In 1968, Kaplow and Goffinet were the first to report a transient decrease of leukocytes in the peripheral blood of patients during dialysis with membranes made from regenerated cellulose [19]. Craddock explained the basic mechanism behind these observations was an activation of the complement cascade by artificial surfaces [20, 21]. The hydroxyl groups on cellulosic membranes were thought to be responsible for this activation because they react with the C3 complement protein, thereby triggering the complement cascade (the concept has since been extended, and is explained in chapter 7 in more detail). The leukopenia and comple-

ment activation observed with the original cellulose membrane provided the platform for the introduction of the biocompatibility concept into membrane development. Since then, each new membrane is not only judged on the basis of its performance characteristics and observable incompatibilities, such as clotting of the fibres, but is also assessed according to its interaction with biological systems (e.g. the complement system); this interaction should be as low as possible or, according to another definition, be considered "appropriate" [22].

Phase III: ß2-microglobulin, ultrapure dialysis fluid, morbidity and mortality of haemodialysis patients – state-of-the-art membranes are highly permeable, biocompatible and synthetic (1986 to now)

In response to the biocompatibility debate, chemical modifications of the cellulose polymer were undertaken with the aim of blunting its immune system activating potential. Hemophan® (di-ethyl-amino-ethyl, or DEAE cellulose), introduced to the market in 1987, is one result of such a modification [23].

Extensive clinical experience has made basic biomaterial researchers, membrane manufacturers and medical scientists aware that no dialysis membrane can be absolutely inert. Based on the experimental work of Lyman et al., Okano et al. and Matsuda et al., a "domain structure" in which hydrophobic and hydrophilic structures are balanced on the membrane surface was accepted as being a beneficial feature regarding membrane biocompatibility; this structure is typical of nearly all biocompatible membranes presently available [24-30]. Adsorption of proteins onto the membrane surface depends on the particular hydrogen bonds, electrical charges and hydrophilic-hydrophobic forces present. The absence of surface nucleophils, such as hydroxyl-groups (as present in regenerated cellulose), a low surface charge and a balanced distribution of hydrophilic and hydrophobic domains appear to characterise more biocompatible membranes [28-30]. Hydrophobic surfaces adsorb proteins and cells, leading to platelet adhesion, whereas hydrophilic surfaces interact with blood cells and activate complement [27]. If an artificial surface exhibits alternating hydrophilic and hydrophobic domains on a nanometer scale (i.e. so that stable interactions with microdomains on cell membranes are not possible), cell activation can successfully be avoided [28-31].

The discovery of ß2-microglobulin (ß2-m) in amyloid deposits of long-term haemodialysis patients, published in 1986 by Geyjo and colleagues, brought another important factor into the discussion on the optimal function of a dialysis membrane [32]. As a protein with a molecular weight of 11,818, ß2-m is removed by high-flux membranes and normally retained with low-flux membranes. Furthermore, some evidence appeared that bioincompatible membranes stimulate ß2-m production [33]. Although the clinical relevance of dialytic ß2-m removal remained a subject of debate, low-flux membranes made from regenerated cellulose came under increasing pressure. Today, evidence exists from clinical data that convective treatment modes involving highly permeable membranes (i.e. haemofiltration and haemodiafiltration) [34, 35] and ultrapure dialysis fluid [36] have a positive impact on the development of dialysis-related amyloidosis: clinical manifestations of the illness are attenuated or delayed by these treatment modes.

In the early eighties, attention began to be focussed on the microbial quality of the dialysis fluid. Henderson, Koch, Dinarello and Shaldon postulated in their "Interleukin Hypothesis" that bacterial products from contaminated dialysis fluid may induce cytokine release in haemodialysis patients, and that this release may be responsible for a number of dialysis-related side effects (e.g. hypotension) [37, 38]. Later, it was proven that the dialysis membrane is not a safe barrier against bacterial degradation products [39, 40]. Transfer of bacterial products from dialysis fluid into blood is particularly easy with high-flux membranes: here the steep pressure drop along the length of the dialyser results in an inversion of the pressure profiles such that, at the end of the dialyser proximal to the blood outlet, dialysis fluid enters the blood. This so-called backfiltration (described in the scientific literature since 1985 [41]) somewhat reduced the enthusiasm for high-flux membranes, and led to the development of low-flux counterparts of well-established, high-flux membrane polymers. Examples are Fresenius Polysulfone®, PMMA and, more recently, Polyamide S™ (now Polyamix™) – all membranes which were primarily developed solely as high-flux membranes. However, even a membrane with small pores is not capable of retaining all microbial products: microbial fragments of molecular weight under 5,000 can pass through low-flux membranes and can also be biologically active [42]. Cytokine generation (measured as interleukin-6 generation) was found to be higher during dialysis with low-flux regenerated cellulose than with high-flux polyacrylonitrile (PAN) when contaminated dialysis fluid was used [43]. The good adsorption capacity of the PAN membrane for microbial fragments (which is also a feature of many other synthetic membranes, e.g. polysulfone and polyamide) explains this observation [44]. This newly-discovered characteristic of some synthetic

membranes opened up a novel application for highly permeable filters: the filtration of dialysis fluid to remove microbial substances that are potentially harmful for the patient. In the beginning, filters normally used for haemofiltration were used as endotoxin filters, but later special filters were developed specifically for filtering the inflowing dialysis fluid prior to its contact with the dialysis membrane (e.g. Diasafe® from Fresenius Medical Care).

Another aspect of biocompatibility is the sterilisation of the dialyser or filter. The first disposable dialysers employed in the nineteen seventies were sterilised using ethylene oxide (EtO). Due to the high content of polyurethane (PUR – the potting compound used in hollow fibre dialysers) which acts as a reservoir for the gas, EtO-sterilised dialysers induced the so-called "first use syndrome" in many patients, i.e. allergic reactions against EtO [45]. The PUR content has since been decreased to a minimum, and times for degassing have been increased to guarantee a safe level of residual EtO. Therefore, EtO-sterilisation has been improved so that dialysers sterilised in this way are still used. γ-irradiation is another cost-effective form of sterilisation; this requires a stabile membrane polymer in order to avoid membrane degradation, as was sometimes reported [46], as well as a particular potting material that does not release carcinogenic methylene dianiline (MDA) [47]. It appears that heat sterilisation is the most "biocompatible" method, but only cellulosic and polysulfone membranes are thermo stable polymers. Thus, this feature added to the excellent performance and biocompatibility characteristics of polysulfone membranes is making them immensely successful; this success is reflected by the fact that most membrane producers have started to develop their own particular polysulfone membrane.

From 1990 on, the quality aspect of dialysis therapy gained more and more importance. There was a rapid increase in the number of publications dealing with quality of life, hospitalisation of dialysis patients, morbidity and mortality (e.g. [48-51]). Initially, the difference in treatment modalities between countries was the main focus of attention [48]; later, interest turned to the influence of reuse on mortality [49]. Since 1994, the dialysis membrane and its impact on morbidity and mortality have been studied intensively, especially with respect to membrane biocompatibility (complement and cell activation, in particular) and permeability (high-flux or low-flux) (e.g. [50, 51]). Hakim and Schiffl reported that acute renal failure patients treated with membranes made from regenerated cellulose had a higher mortality rate than patients treated with synthetic membranes [52, 53]. Although these results were not confirmed in a later controlled, prospective, multicentre study of Jörres et al. [54], such studies inflamed a controversy in which various study

designs were heavily criticised (e.g. [55]). Whereas the special group of acute renal failure patients is the focus of the above-cited studies, other investigations reported increased mortality for chronic haemodialysis patients when treated with low-flux rather than high-flux membranes (both polysulfone dialysers [56, 57]). However, the conditions under which such results were generated must be carefully analysed: patient collectives and treatment conditions (especially dialysis adequacy) must be comparable, and, ideally, membranes of the same polymer family should be used. Further insight into the possible benefits of using biocompatible, high-flux membranes regarding patient morbidity and mortality was expected, to be supplied by clinical trials, such as the HEMO study in the US (e.g. [58]) and the still ongoing MPO study in Europe [59]. The HEMO study failed to show any difference between low-flux and high-flux membranes (both biocompatible) with respect to mortality, but there are many points of criticism regarding study design etc. [60, 61]. Fact is, however, high-flux, synthetic membranes are now the most commonly used membranes, having long displaced the once predominant low-flux membranes made of regenerated cellulose (mainly Cuprophan®). In 2001, 55% of all membranes used in the USA, Japan and Europe were synthetic membranes and 50% of *all* membranes used were high-flux membranes [62]. These numbers increased again in 2002, i.e. worldwide numbers of high-flux and synthetic dialysers sold increased by 19% and 20%, respectively [63].

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2. Membrane family overview and nomenclature

A wide spectrum of haemodialysers and filters together with a multitude of different membranes are currently available commercially. In the year 2002, more than 1000 different dialyser types with membranes made from at least 10 different polymer materials were on the market (see appendix: list of haemodialysers and **table 2.1**). Few would have the time to survey all the different types in order to evaluate the actual situation regarding membrane nomenclature. This chapter is intended to provide insight into the frequently inconsistent and confusing nomenclature of different membrane polymers and the various descriptions given.

The polymer essentially determines the chemical and physical behaviour of a dialysis membrane: the final dialyser sterilisation mode, resistance against chemical agents used during possible dialyser reprocessing, and device biocompatibility are all influenced by the type of polymer used to produce the membrane. The earliest dialysis membranes were manufactured from regenerated cellulose or cellulose acetate, originating from the spinning expertise of the textile industry. The ideal polymer for dialysis should enable the production of a biocompatible membrane family whose members are of considerable physical strength, have excellent diffusive and, where appropriate, convective properties, and have performance and biocompatibility profiles which are resistant to all chemicals and sterilising agents used in haemodialysis procedures, including heat sterilisation (121°C). In addition, recent literature demonstrates the importance of ultrapure dialysis fluid for the attenuation of long-term clinical consequences [1, 2]. Therefore, whenever ultrapure dialysis fluid cannot be guaranteed, as is still the case in many clinics, it is vital that modern haemodialysis membranes should adsorb endotoxins at the outer surface, as this provides added protection against transfer of bacterial derivates from the dialysis fluid to the patient in case of microbial contamination of the dialysis fluid.

Cellulosic		Synthetic		
Regenerated cellulose	**Modified cellulose**	**Polysulfones**	**Poly(aryl)ether-sulfones**	**Others**
Cuprophan® (Membrana)	CDA, Dicea (Teijin, Toyobo)	Fresenius Polysulfone® (FMC)	PEPA® (Nikkiso)	AN69®, AN69ST (Hospal)
Cuprammonium rayon (Asahi, Terumo, Teijin)	CTA, Tricea (Toyobo)	Helixone® (FMC)	Polyamix™ (PolyamideS™) (Gambro)	PAN (Asahi)
SCE (Teijin)	Hemophan® (Membrana)	α Polysulfone (Saxonia, B.Braun)	DIAPES® (Membrana)	PMMA (Toray)
G-O-P DIAFIL® (Renaselect*)	SMC® (Membrana)	Toraysulfone® (Toray)	Arylane (Hospal)	EVAL® (Kawasumi)
	PEG-RC (Asahi)	APS® (Asahi)		Polyamide (Gambro)
	Excebrane (Terumo)			

Table 2.1: Main dialysis membranes currently on the market. *SCE = saponified cellulose ester; CDA = cellulose diacetate; CTA = cellulose triacetate; Hemophan® = diethylamminoethyl cellulose; SMC® = benzyl cellulose = Polysynthane; PEG-RC = polyethyleneglycol grafted regenerated cellulose; EVAL® = ethylvinylalcohol copolymer; Excebrane = vitamin E coated regenerated cellulose; PAN = polyacrylonitrile; PEPA® = polyethersulfone / polyarylate; DIAPES®, Arylane = polyarylethersulfone syn. polyethersulfone, FMC = Fresenius Medical Care, *Renaselect former Gross-O-Pharm.*