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The scientific principles and technological determinants of haemodialysis membranes

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ABSTRACT

In most biological or industrial (including medical) separation processes, a membrane is a semipermeable barrier that allows or achieves selective transport between given compartments. In haemodialysis (HD), the semipermeable membrane is in a tubular geometry in the form of miniscule pipes (hollow fibres) and separation processes between compartments involve a complex array of scientific principles and factors that influence the quality of therapy a patient receives. Several conditions need to be met to accomplish the selective and desired removal of substances from blood in the inner cavity (lumen) of the hollow fibres and across the membrane wall into the larger open space surrounding each fibre. Current HD membranes have evolved and improved beyond measure from the experimental membranes available in the early developmental periods of dialysis. Today, the key functional determinants of dialysis membranes have been identified both in terms of their potential to remove uraemic retention solutes (termed 'uraemic toxins') as well subsidiary criteria they must additionally fulfill to avoid undesirable patient reactions or to ensure safety. The production of hundreds of millions of kilometres of hollow fibre membranes is truly a technological achievement to marvel, particularly in ensuring that the fibre dimensions of wall thickness and inner lumen diameter and controlled porosity—all so vital to core solute removal and detoxification functions of dialysis—are maintained for every centimetre length of the fragile fibres. Production of membranes will increase in parallel with the increase in the number of chronic kidney disease (CKD) patients expected to require HD therapies in the future. The provision of high-quality care entails detailed consideration of all aspects of dialysis membranes, as quality cannot in any way be compromised for the life-sustaining—like the natural membranes within all living organisms—function artificial dialysis membranes serve.

Keywords: haemodialysis, hollow fibres, membranes, semipermeable, transport phenomena

CONNOTATIONS ASSOCIATED WITH 'MEMBRANES'

The comprehension of a 'membrane' is often confounding given the multifarious types that exist within all organisms as well as those not resulting from natural sources [1–7]. Though conceptually both categories serve the same overall purpose, man-made membranes bear little resemblance to biological membranes in terms of either topography, complexity or their mode of action.

The term 'membrane' generally evokes the impression of a (thin) barrier, layer or boundary that separates two compartments having variable composition or amounts of constituents. The units of life, cells, are defined by membranous boundaries; in the absence of these perimeters, life may not have begun [1, 8]. Communication between the compartments separated by these boundaries—transport of substances across this barrier—is facilitated by a combination of the physicochemical structure and properties of the membrane and driving forces (passive

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and active transport) that determines the direction and extent of transport of specified components [2, 4–7].

In most biological or industrial (including medical) separation processes, a membrane is a semipermeable barrier that allows or achieves selective transport between given compartments [6, 7]. The cell (or plasma) membrane that surrounds every living cell and organelles within (e.g. nucleus, mitochondria, chloroplasts) is a highly dynamic, multicomponent assembly involving smaller functional units carrying out extraordinarily complex biochemical transport and exchange functions according to the tissue or organ they are part of [1, 9–14]. It is not uncommon, especially in medical applications involving the use of membranes, to assert that a particular man-made membrane and the function it serves 'mimics' the natural membrane or the organ function it attempts to substitute. Such extravagant comparisons and superficial claims do little to add credibility to a cause, and often reflect an attempt to gain marketing or commercial advantages [15]. Few having an appreciation of the marvel and intricacies of biological membranes would place them on the same pedestal as monofunctional man-made entities that are intended simply to separate or purify components.

Distinctiveness of membranes in dialysis therapies

For new entrants into the field of dialysis, it is not easy to discern certain aspects of the membrane those already in the field may consider axiomatic. In one form of dialysis therapy [peritoneal dialysis (PD)] separation is achieved by means of a biological membrane (the peritoneum) already present within the body, while in the other modality [haemodialysis (HD)] the membrane is mass-produced in sophisticated manufacturing processes and facilities. Both HD and PD achieve similar overall objectives in terms of cleansing the blood of renal failure patients, yet each involves different patient considerations and results in variable clinical outcomes over time and are apparent particularly when patients are switched from one modality to the other [16–20]. Further, the glomerular filtration barrier of the natural kidney and the peritoneal membrane, though both biological, have distinctly different structure–function relationships and size selectivity [21]. The former is an anatomical unit whose function is to remove waste and excess substances from the blood, producing urine; the latter is a membrane lining the abdominal cavity to support organs within it and has no physiological waste removal function, but its semipermeable nature and microvasculature has been harnessed for dialysis in end-stage kidney failure (ESKD) patients [22–25].

For both HD and PD, the aforementioned 'driving forces' that are necessary to achieve selective separation are created by the applied conditions, whether using biological membranes (as in PD) or with man-made semipermeable membranes (in HD). The two driving force principles, diffusion and convection (i.e. process by which solutes are dragged by fluid movement, or ultrafiltration, caused by osmotic and/or hydrostatic forces), facilitate transport processes in nature as well as in 'artificial' systems. Concentration gradient–dependent diffusion is the primary driving force for both conventional HD and in PD, which involves an osmotic force driving removal of water by convection [18]. Non-biological membranes are generally visualised as a thin flat barrier, layer or envelope that separates, protects or keeps entities apart [7, 26]. In HD, the semipermeable membrane is in a tubular geometry in the form of miniscule pipes (hollow fibres) and separation processes between compartments involve a complex array of scientific principles and factors that influence the quality of therapy a patient receives. Several conditions need to be met to accomplish the selective and desired removal of substances from blood in the inner cavity (lumen) of the hollow fibres across the membrane wall into the larger open space surrounding each fibre [26, 27].

Membranes in dialysis prior to modern hollow fibre membranes

A voluminous body of literature describing the evolution of dialysis membranes is available [28, 29]. Like most accounts detailing the historical journey of technological advancements or inventions leading to their present-day status quo, such reviews make engrossing reading [30, 31]. From the early application of the most rudimentary of materials (including natural membranes from animals) and forms to the modern man-made high-technology hollow fibres, the journey of membranes has been one full of enterprise [32]. From the first description of the term 'dialysis' (as a separation/transport process) in 1861 by Thomas Graham to a therapy form that today bears the name of the transport phenomenon, the history of the evolution of membranes is one of resolute pioneering [31, 32]. Although the scope of this supplement is to provide insight into the therapy-defining determinants of hollow fibre membranes used in renal replacement therapies (RRTs) today, insights into the early search for a suitable semipermeable membrane would nevertheless be of value [28–34]. To fully derive an appreciation (and limitations) of hollow fibre HD membranes, the analogous membrane apparatus of the natural kidney—whose detoxification function man-made membranes attempt to replace—needs to be considered.

'Filtration membrane' of natural kidney and hollow fibre membranes in dialysis

Ridding blood of unwanted substances (by-products of metabolism) is just one of several life-sustaining functions of the healthy natural kidney. Some of the more specific and vital (physiological) functions include control of blood pressure, producing the hormone erythropoietin, activating vitamin D and maintaining the acid–base, electrolyte and body fluid balance. In chronic kidney disease (CKD), impairment of multiple physiological and metabolic pathways progressively leads to ESKD [35, 36]. This includes conditions such as hypertension, diabetes, anaemia and dyslipidaemia, which lead to increased risk of cardiovascular disease (CVD). Together with nutrition–metabolic dysfunction and hormonal malfunctions, CKD is thus a complex and debilitating multicomorbid disease state associated with high morbidity and mortality mostly related to CVD [37, 38].

However, it is the impairment of the filtering function of the kidney (removal of 'waste' products and excess fluid) that singularly leads to a rapid and severe deterioration of health [39]. Progressive loss of this function is commonly categorised in stages 1–5 of CKD based on the level of the estimated glomerular filtration rate (eGFR) normalised to body surface area and derived from serum creatinine measurements [35, 36, 40]. Stage 5, whereby residual renal function assessed by the eGFR falls below 15 ml/min/1.73 m2, is commonly regarded as ESKD, necessitating RRT [41]. Given the scarcity worldwide of kidneys for organ transplantation, dialysis (HD or PD) remains the only RRT option for ESKD patients. HD is prescribed to ~80% of patients on dialysis [42].

The anatomical apparatus that performs the primary filtration function is in the part of the nephron that is in the cortex region of the kidney [43]. A tuft of capillaries (the glomerulus)

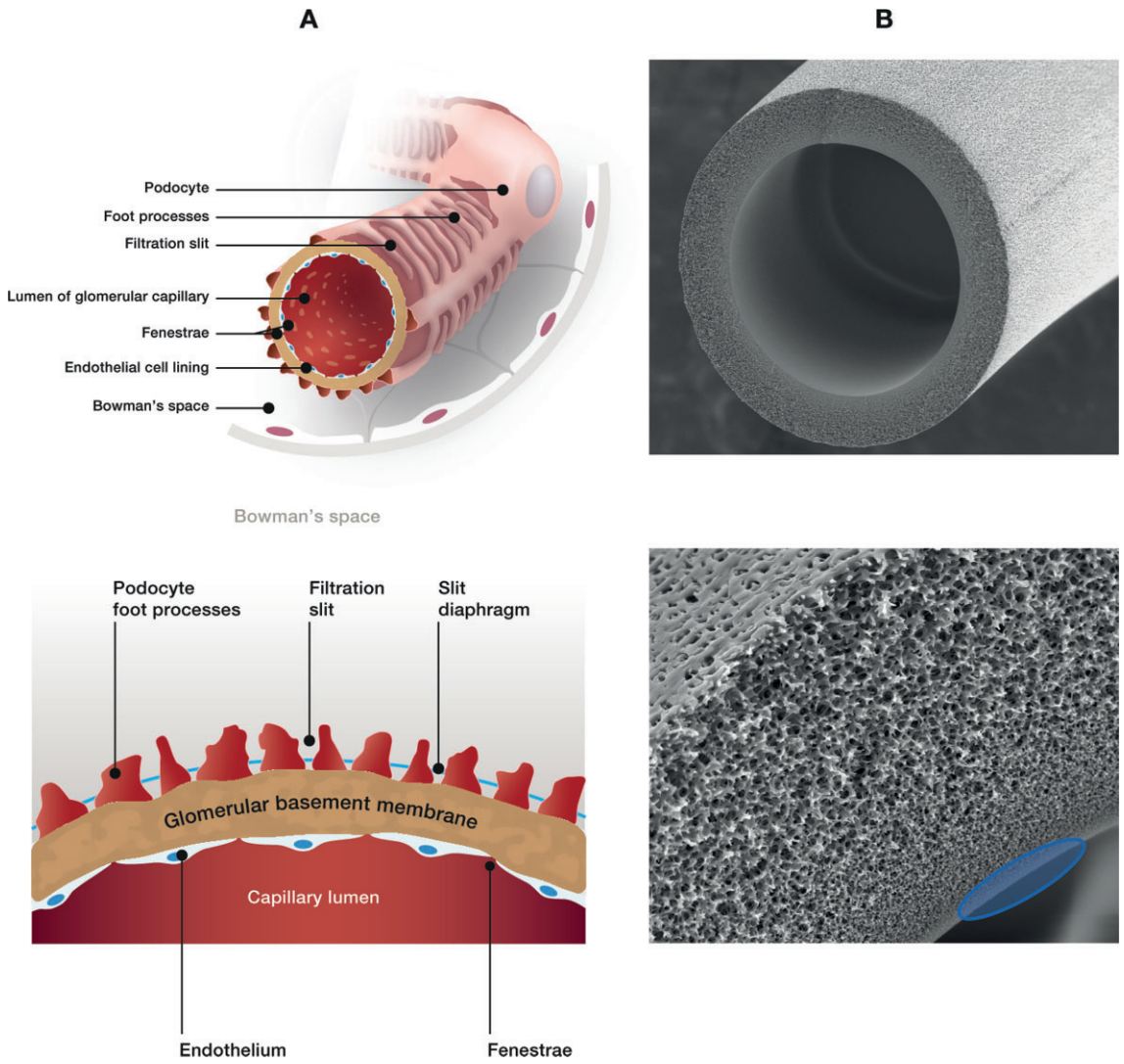

FIGURE 1: Filtration apparatus of the renal corpuscle of the nephron in the natural kidney (*A*) compared with the porous, sponge-like structure of man-made hollow fibre membranes of the artificial kidney (*B*; scanning electron microscopy images). Blood cells are unable to pass through the endothelial fenestrations, while most plasma proteins can traverse this initial barrier. The three-layer non-cellular matrix that constitutes the GBM then restricts passage of proteins based on size–charge criteria. Thereafter, the slits created by the interlocking foot-like protrusions of the podocytes that surround the capillaries restrict passage of proteins up to ~70 kDa (including albumin) into the glomerular space (*A*). In hollow fibre membranes of the artificial kidney (*B*), the sieving properties (that involve mean pore size and distribution) of the thin (<50 nm) innermost blood-contacting region (highlighted in blue) are the sole determinants of what can, or cannot, pass across the entire thickness (width) of the membrane wall.

encapsulated by the cup-shaped, double-walled dilation known together as the renal corpuscle (Bowman's capsule), carry out the filtration. The formation of urine entails the accumulation of an ultrafiltrate of plasma (containing water and small molecules, smaller than albumin) from the blood into the urinary (or capsular) space of the Bowman's sack. The glomerular basement membrane (GBM) is often erroneously thought of as the separating counterpart of semipermeable membranes of dialysis therapies, but it is just one component of the complex renal corpuscle filtration machinery. The selective separation achieved in the natural kidney involves other distinct anatomical structures (e.g. podocytes and their slits of variable sizes created by the foot-like processes, endothelial fenestra) and a degree of sophistication that goes far beyond simple pore-centric perceptions of semipermeable membranes (as a monolayer with physical perforations).

Figure 1A (left panels) depicts the apparatus of the natural kidney involved in the (selective) filtration of components from the blood side (capillaries of the glomerulus) to the urinary space of the Bowman's capsule. Several membranous layers are involved. Beginning from the capillary side of the glomerulus (bringing in the blood for detoxification), the first separation barrier is the gap (fenestrations) between the endothelial cell monolayer. This is followed by the three-layer non-cellular matrix that constitutes the GBM—laminas rara interna (adjacent to endothelial cells of capillary), lamina densa (in the middle) and lamina externa (adjacent to the Bowman's space). The lamina externa of the GBM is wrapped by podocytes (from the visceral epithelial lining of Bowman's capsule) via their network of pseudopodial protrusions. The adjoining pseudopodia, or foot-like processes, have numerous filtration slits (known as slit pores) between them. A thin diaphragm between the slits acts as a

final filtration barrier before the fluid enters the glomerular space [21].

Thus the fusion of the GBM, capillary endothelia cells and the podocyte filtration slits (renal corpuscle) constitutes the physical glomerular filtration apparatus of the natural kidney. In the first step, endothelial fenestrations (pores between 70 and 100 nm) retain blood cells but permit the passage of various plasma proteins, solutes and fluid. Next, the three layers of the GBM prevent access of larger proteins (including albumin) by a combination of charge and size restrictions to the tubular lumen space; this is also the main site of restriction of water flow. Finally, the interdigitate slits between the pseudopodia of podocytes play an active role in preventing plasma proteins from entering the urinary ultrafiltrate by providing the third restrictive barrier (depicted in Figure 1A, left panels). Thus formation of glomerular ultrafiltrate is dependent on the interplay of glomerular pressures and flows, as well as the intrinsic permselectivity properties of the glomerular capillary wall. These intrinsic permeability properties serve to exclude macromolecules from the urinary space, based on size as well as by net molecular charge discrimination [44].

Figure 1B (right panel) shows the typical geometry and structure of hollow fibre membranes used in the artificial kidney (HD). Any substance that can pass through the thin, innermost separating region (the 'skin' layer; <50 nm) is able to pass through the rest of the membrane wall. The fallacy of claims that man-made membranes mimic the natural kidney's filtration apparatus is apparent: both may achieve the same overall objectives, i.e. the removal of unwanted waste substances from the bloodstream, but that is where the analogy ends. The glomerulus produces the primary urine by filtering blood and retains larger proteins, including most serum albumin (molecular weight >67 kDa). Proteins with a molecular weight <60 kDa usually pass freely through the GBM and are actively reabsorbed within the tubular system [45, 46]. With dialysis membranes, if the membrane mean pore size is larger than that of albumin, it leaks out into the dialysate and controlled or highly selective removal of individual proteins is neither backed by definitive evidence nor possible. As will be discussed later, the selectivity of removal of substances of different molecular size is achieved through altogether different approaches in HD membranes.

THE MAKING OF HOLLOW FIBRE MEMBRANES FOR RENAL REPLACEMENT THERAPIES

Unsophisticated as man-made dialysis membranes may seem in relation to the natural separation counterpart within the nephron, the hollow fibre membrane used in RRTs is nevertheless a work of considerable technical accomplishment of materials science and engineering. The accomplishment involves, first, converting solid polymer materials (either available in nature or synthesised in the laboratory) into minute pipe-like structures. The second is the creation of defined structural attributes that permit semi-selective separation of biological entities having a broad size range. Third, the chemical composition of the materials selected must be such that there is minimal unfavorable interaction with a unique tissue that serves every organ and cell of the human body—blood. Finally, every centimetre of the tens of millions of kilometres of hollow fibre membranes manufactured annually to satiate the need of providing lifelong treatment for a growing number of ESKD patients must, as part of a medical device, meet defined and stringent quality and safety criteria. Before the advent of hollow fibre membranes, large diameter tubing made from collodion, coils of cellophane (Visking) tubing and flat sheet membranes were in use in the early pioneering period of dialysis [28, 30–32]. As blood flows more easily in tubular conduits (like in the vasculature of the body), the geometries (and materials) of early devices impeded progress in the development of the 'artificial kidney'. Thereafter, membrane spinning technology expedited advances in the evolution of dialysis therapy.

The feat of producing medical hollow fibre membranes on a large scale

The choice of the materials used, the manufacturing conditions, resultant morphology and dimensions of the tubular membranes as well as surface physicochemical properties all impact the efficiency of detoxification of blood, patient well-being and long-term clinical outcomes. An appreciation of the basic elements of hollow fibre membrane production would enable a more informed assessment of the possibilities and constraints of current extracorporeal RRTs. The pressing need for new or improved dialysis membranes is often voiced by clinicians; over a period of 4 decades, the authors have encountered several well-meaning and creative propositions that seldom reach fruition, as they fail to meet one or more of the myriads of technical, biomedical, safety and regulatory requirements that need to be fulfilled for a functional medical device. Further, realisability of many new concepts is impeded by considerations involving investment in research and development, sustainability and economy of scale during manufacturing processes of membranes.

The hollow fibre membrane spinning technology of HD membranes. Manufacturing of dialysis membranes is intricately linked to the spinning of yarn (thread made of natural or synthetic fibres) for use in weaving of textiles, curtains, carpets, etc. In fact, until recently, one of the most frequently used hollow fibre dialysis membranes, Cuprophan, was developed and produced in the 1970s by one of the world's leading manufacturers of fibres for clothing, household fabrics and industrial applications, ENKA (Obernburg, Germany) [47, 48]. However, yarn is a 'solid' tubular structure and membranes for RRTs necessitated the creation of a hollow circular space ('bore' or lumen) within the 'thread' for blood to flow through and surrounded by a semipermeable structure for selective transport. As hollow fibres are self-supporting structures, their dimensions (wall thickness relative to lumen diameter) are crucial for stability. There are three types of processes used to prepare hollow fibre membranes and capillaries [49]:

- melt spinning: the polymer is heated above its melting point and the liquid polymer extruded through a spinneret. By immediate cooling, a phase transition occurs, and the polymer solidifies, forming a capillary (hollow fibre) of uniform structure.
- dry spinning: the polymer is dissolved in a very volatile solvent. After extrusion, the polymer solution is heated and, because of evaporation of the solvent, the polymer solidifies.
- wet spinning: a polymer solution is pumped through an orifice and a filament is continuously drawn and simultaneously solidified in a non-solvent bath where demixing occurs because of the exchange of solvent and non-solvent. Between the spinneret and the non-solvent bath there is an air gap where membrane formation starts.

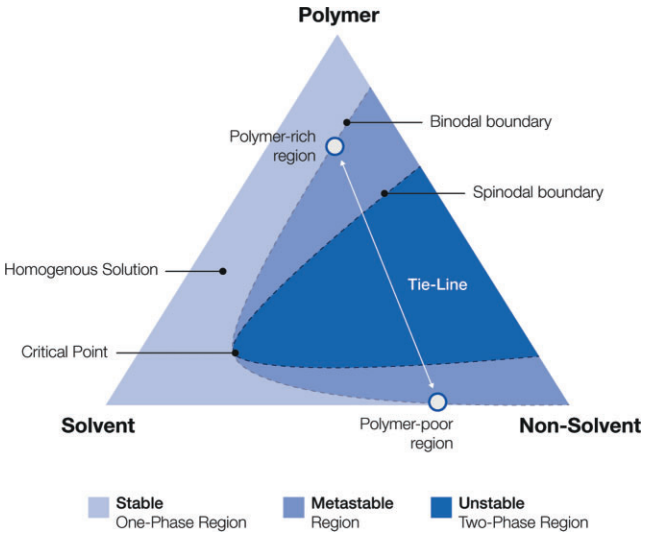

FIGURE 2: The ternary phase separation system for the manufacture of hollow fibre hemodialysis membranes involving three components (polymer, solvent, non-solvent). The binodal boundary separates phases whereby thermodynamic conditions are such that the polymer–solvent solution is either fully mixed (homogeneous and stable) or components still coexist but begin to separate because of the addition of non-solvent (metastable state; light blue region). When material moves into the unstable spinodal region, decomposition occurs, resulting in separation into distinct phases with different chemical compositions and physical properties (dark blue region). A tie line connects any two points to indicate either polymer-rich or polymer-lean areas. Essentially, the addition of non-solvent to homogeneous solution (polymer + solvent) 'extracts' the solvent to leave behind a scaffolding with sponge-like structure.

Membranes for RRTs are predominantly wet spun, as the processes are more versatile, enabling any desired membrane morphology through variation of any of the different parameters involved in this technique. With careful control of the conditions, the wet spinning process is especially suited for the preparation of a thin-skinned top layer having the desired degree of porosity [50].

Phase separation of polymer systems define the structural determinants of membranes. Phase separation (or phase inversion) is the basic principle of membrane formation whereby a polymer is transformed in a controlled way from a liquid to a solid state [7]. The process of solidification is usually initiated by the transition from one liquid state into two liquid states (liquid–liquid demixing). Phase inversion is a physical phenomenon whereby a polymer dissolved in a continuous phase solvent system (i.e. a solution) inverts into a solid macromolecular network in which the polymer becomes the continuous phase. It is performed by removing the solvent from a liquid–polymer solution by adding a non-solvent, leaving a porous, solid 'scaffolding'. The aim is to create the desired membrane structure that is suitable for a specific separation application and is achieved by selecting appropriate polymers and controlling various conditions of the process. Most membranes for use in RRTs are based on a ternary phase separation system, i.e. involving three components: a polymer, a solvent and a non-solvent represented as an interconnected triangle or triad (Figure 2).

The corners of the triad represent the pure (100%) components; any point on one side of the triangle represents a mixture of the two components on the axis, and any point within the triangle denotes a mixture of the three components. All phase inversion processes are based on the same thermodynamic principles and the starting point in all cases is a thermodynamically stable solution that is then subjected to 'demixing' [7].

The overall stages of the actual manufacturing are:

Stage I. This stage involves preparation of a homogeneous solution, i.e. polymer dissolved in a solvent (both must be miscible with each other). The exact location on the polymer–solvent axis indicates the composition of the solution, i.e. the relative amounts of polymer and solvent. This 'casting' solution normally comprises more than one polymer, as additional additives ('copolymers') are required to derive specific application-dependent characteristics of the membrane. For the manufacture of most dialysis membranes, polyvinylpyrrolidone (PVP) is used as a copolymer. PVP serves not only as a 'pore-forming agent' to obtain an open, interconnected porous membrane structure, but also to provide a membrane surface having an 'optimal' hydrophobic–hydrophilic balance that is required for biocompatibility [7, 48].

Stage IIa. This stage involves the addition of a non-solvent to initiate demixing so that the solution becomes thermodynamically unstable. The boundary of the stable–unstable region is represented by the binodal curve denoting the condition at which any two phases may coexist to initiate the formation of a sponge-like, porous structure, shown in Figure 1.

Stage IIb. In practice, Stage IIa is coupled with the step of creating a 'bore within the rod-like fibre' (the lumen or the blood compartment) by using a high-precision spinneret (made of ceramic or titanium) having two concentric chambers (Figure 3). By pumping non-solvent through the inner orifice of the spinneret and polymer solution (polymer + solvent) in the outer chamber while immersing both into a precipitation bath containing non-solvent, a 'hollow fibre' having defined dimensions results. Figure 4 depicts these fundamental stages of membrane making.

The versatility of the entire manufacturing pathway, from the starting homogeneous solution, precipitation, solidification to form different membrane structure within the phase separation triangle, is shown in Figure 5. Variable membrane structures can be derived from either a single starting or polymer casting solution as shown in Figure 5, or from different starting solution compositions (Figure 5B). Depending on the precise conditions selected, different precipitation pathways within the triangle result in totally different membrane morphologies and hence distinctly different separation characteristics [7]. One is therefore able to derive membranes that are more 'polymer-rich' (on the polymer–solvent axis) or those where there is a higher solvent content and therefore less polymer, resulting in either a more 'dense' or more 'porous' membrane structure, respectively.

Stage III in Figure 6 shows several additional steps involved in the processing of the hollow fibres after completion of the phase separation stages I and II. The fibres are rinsed repeatedly in water, dried, given a wavy form to facilitate free dialysis fluid flow around individual fibres within the bundle and coiled several times around a wheel (according to the number of fibres for a particular dialyser). Note the reprocessing and regeneration of fluids used in the manufacturing processes for reuse.

Polysulfone membranes, or polymers from the polysulfone family (e.g. polyethersulfone/polyarylethersulfone), are the most frequently used membranes to treat end-stage CKD patients worldwide on HD [51–54]. To help understand the scientific principles and technological procedures involved in membrane making, Figure 7 summarises the composition of the key

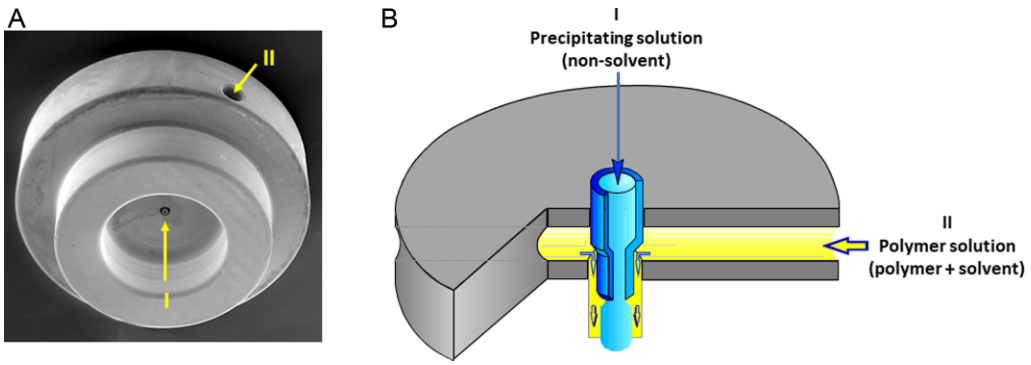

FIGURE 3: Photograph (**A**) and schematic cross-section (**B**) of the high-precision spinning nozzle (spinneret) used for the production of hollow fibre dialysis membranes. The nozzle comprises two chambers, an inner (I) and an outer (II). By pumping non-solvent through the inner orifice (chamber I) of the spinneret and polymer solution (polymer + solvent) in the outer chamber (II) and simultaneously immersing the exudate into a precipitation bath that also contains the precipitating solution (non-solvent), ternary phase separation processes (as shown in Figure 2) result in the formation of porous structures within the membrane. The dimensions of the inner orifice of chamber I of the nozzle determines the dimensions (wall thickness and inner lumen diameter) of the hollow fibre membrane.

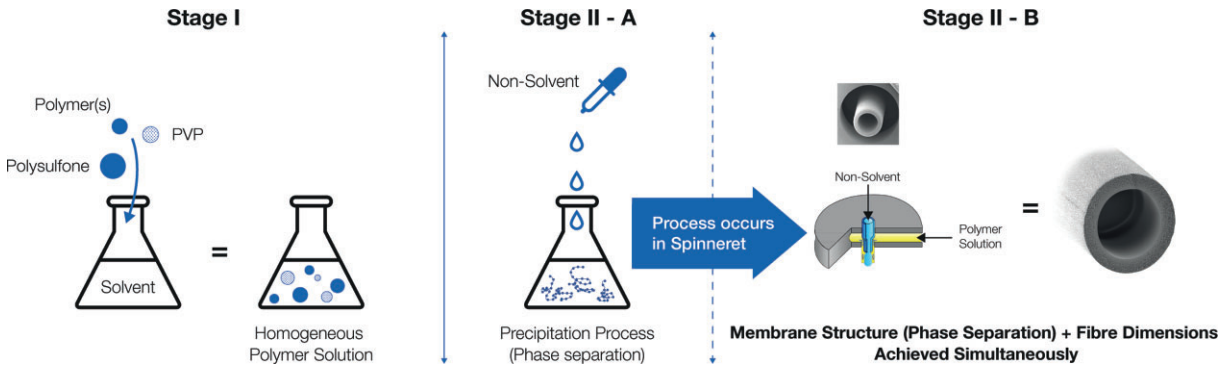

FIGURE 4: Schematic summary of the overall stages involved in the making of HD membranes. The manufacturing process begins by dissolving core polymer (polysulfone) granules and copolymer solution (PVP) in a solvent to form a solution (stage I). The addition of non-solvent to induce precipitation (stage II - A) culminates in 'phase separation' (stage II - B) to derive the final porous structure of the hollow fibre membrane wall. The precise construct of the spinneret defines the fibre dimensions (wall thickness and lumen diameter) which, together with the porosity of the membrane wall, determine the solute (uremic toxin) removal capabilities of a particular dialysis membrane.

chemical components typically used for the manufacture of polysulfone-based dialysis membranes.

Key membrane production-related aspects that influence HD therapy. Three aspects of membrane making essentially determine the type of membrane produced and the eventual extent to which uraemic toxins are removed and other secondary features that membranes must possess: the choice of the main polymer, the choice and concentrations of the copolymer(s) and the membrane spinning conditions and parameters selected during production:

(i) By far the most important aspect of membranes for RRTs is the choice of polymer(s) used—it essentially defines the overall 'personality' (detailed below) of the membrane, influencing manufacturing processes and performance-related parameters. The composition of the polymer mixture, the thermodynamic conditions selected for the phase separation process as well as the physical dimensions of the spinneret determine membrane characteristics that define therapy quality. Together with the therapy modality and related treatment conditions selected based on the individual patient's needs and clinical profile (including comorbid conditions), membrane features eventually influence patient well-being and long-term outcomes [55, 56].

(ii) Although dialysis membranes are normally referred to and defined by their main polymer constituent, copolymers are required to obtain an open, interconnected porous structure. PVP is a common additive in most dialysis membranes [48]. It has the dual purpose of affecting the physical (morphology) and chemical properties (conferring a degree of hydrophilicity to hydrophobic polymer systems) of the membranes [57, 58]. The latter (hydrophobic–hydrophilic balance) defines the biocompatibility (i.e. surface chemistry) profile of membranes [59, 60].

(iii) Membrane manufacturing stages described in the previous section are based on complex and reciprocal relationships between thermodynamic as well as kinetic factors during phase separation. These relationships involving chemical aspects (polymer composition and chemistry, solvents, non-solvents) as well as physical attributes (such as spinneret dimensions, speed, temperature, viscosity, humidity, pressure, residence time with air, mass transfer) ultimately determine the overall profile of the membrane that then eventually impacts the therapy and patient outcomes. It must be emphasized that while structural attributes

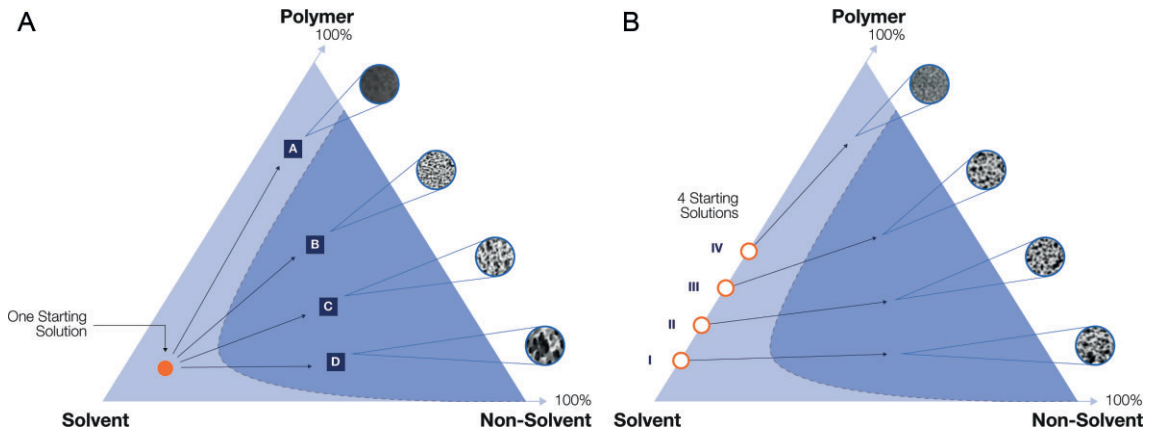

FIGURE 5: The two general approaches of tailoring the structure and porosity of dialysis membranes: (**A**) by selecting a single polymer–solvent composition (red dot) for the initial spinning solution (i.e. along the polymer–solvent axis) and different thermodynamic conditions or pathways during the spinning processes (e.g. A–D), the desired membrane structure (and its solute removal characteristics) is achieved. These could range from fully sponge-like structures to the less desirable finger-like or vacuole-shaped open spaces. (**B**) Different membrane structures having distinct solute-removal capabilities can also be derived by selecting variable starting solutions (i.e. different polymer–solvent compositions; open red circles I–IV) and appropriate thermodynamic conditions for each pathway.

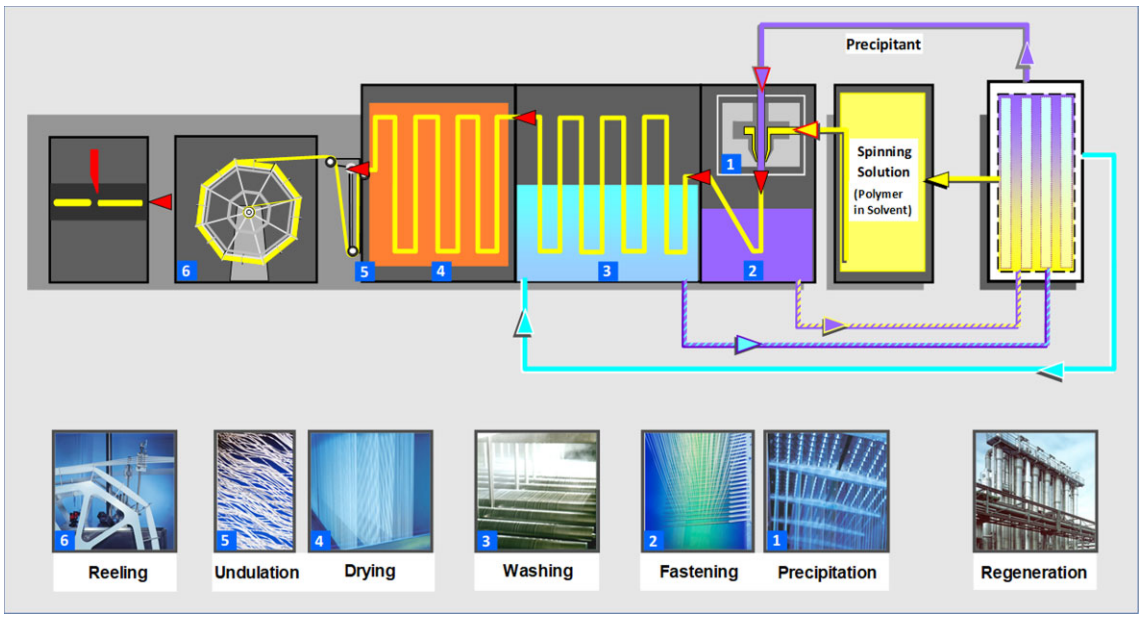

FIGURE 6: Several additional steps are involved in the production of the hollow fibres after completion of the main phase separation stages (1) and fastening (2). The fibres are rinsed repeatedly in water (3), dried (4), the fibres made wavy (undulation); (5) for free dialysis fluid flow around individual fibres within the fibre bundle and finally wound several times around a wheel (according to the desired number of fibres to be inserted within a particular dialyser type); (6). Note the reprocessing and reuse (regeneration) of several fluids used in the manufacturing process.

(pore size, distribution, etc.) are of primary importance in dialysis, several factors (secondary requirements and constraints, e.g. sterilisability, biocompatibility or adsorption of endotoxins) need to be considered at the outset of the manufacturing process for dialysis membranes [61].

There are two categories of membranes based on their wall structure, i.e. from the lumen side to the outer wall, symmetric and asymmetric [62–64]. In symmetric membranes, the morphology from the inner to the outer wall is uniform in terms of pore size and distribution and degree of porosity. For asymmetric membranes, the inner region of the membrane has a thin separating region of high polymer density and the remainder of the membrane wall is a more porous sponge-like structure with lesser amounts of polymer [63, 64]. Most membranes used in routine HD today are asymmetric.

Membrane features that impact HD therapy

Manufacturers select materials and spinning conditions to derive membranes with desired characteristics; membrane structure (morphology), fibre dimensions and physiochemical (surface chemistry) properties of the inner (blood-contacting) and outer surfaces are the key therapy-defining determinants of dialysis membranes.

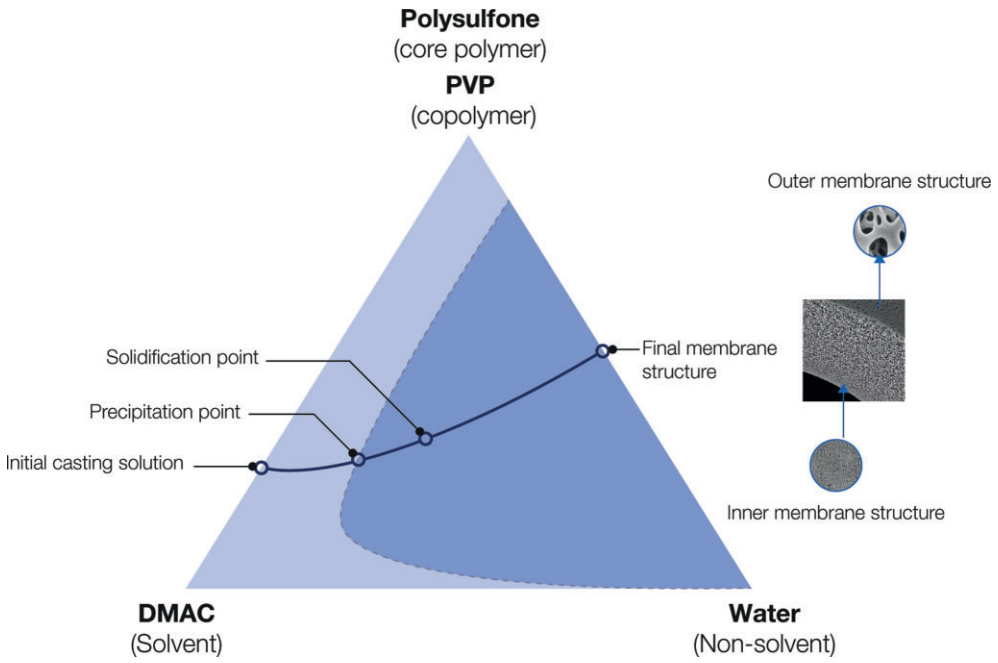

FIGURE 7: The making of asymmetric polysulfone membranes by ternary phase separation principles. Most HD membranes in current use are polysulfone based. Typically the spinning solution (initial casting solution) is prepared by dissolving a mixture of polysulfone as the core polymer and a copolymer (PVP) in dimethylacetamide (DMAc) as a solvent. Precipitation and solidification, as explained in the text, are achieved by using water as the non-solvent. The precise thermodynamic conditions used for the membrane spinning process determine the final membrane structure. The thin, inner blood-contacting region as well as the wall thickness and inner lumen diameter of the hollow fibre membrane collectively determine the solute transport (uremic toxin removal) characteristics of haemodialysers.

Impact of membrane morphology on therapy: determining transport phenomena. Membrane morphology (wall structure) is the central feature that defines separation efficiency [26, 27, 48]. In dialysis, as with ultrafiltration membranes having an asymmetric structure, the pore size and distribution at the inner (lumen) blood-contacting side play a decisive role [58, 65]. The innermost layer determines the initial resistance to transport (diffusive or convective), and any solute that is able pass through (based on its size relative to the mean pore size) would be able to traverse the rest of the thickness of asymmetric membranes [66]. Thus the pore size of the inner layer and the degree of porosity of the remainder of the membrane determine the transport ('performance') characteristics of membranes: hydraulic permeability (ultrafiltration), clearance and sieving properties (discussed in a subsequent article in this supplement).

Structural considerations of membranes are of historical significance in the evolution of dialysis. In the early experimental days of HD, the membranes available to researchers were cellulose-based, first as flat sheets and later as hollow fibres [31, 32]. The large wall thickness (up to 300 μm) resulted in poor removal of uraemic retention solutes; as diffusion, the primary mechanism of transport across dialysis is directly dependent on the membrane thickness as defined by Fick's equation, elimination of larger molecular substances in particular was severely restricted [67]. This observation led eventually to the proposal of the landmark 'middle molecule hypothesis' that provided the impetus for a better understanding of toxicity in uraemia [33, 34, 68–70]. It also led subsequently to the development first of thin-walled cellulosic membranes (10 μm) to facilitate diffusion and later to synthetic membranes capable of withstanding higher ultrafiltration rates necessary for the convective removal of large-sized uraemic retention solutes that accumulate in blood in ESKD.

Impact of physical attributes of fibres on flow-dependent transport phenomena. Morphological features are not the only determinants of hollow fibre membranes that influence the efficiency of solute transport during HD. The diameter of the fibre lumen affects the flow characteristics of blood within each fibre, influencing transport phenomena and hence overall device performance [71, 72]. A decreased hollow fibre inner diameter alters pressure profiles that results in maximised internal filtration, a phenomenon that occurs with that of backfiltration and increases large solute clearance [72]. As blood rheology is known to affect mechanisms like thrombosis within the body, the impact of fibre geometry has been studied with respect to biocompatibility of dialysers [73].

Impact of inner surface chemistry on blood material interactions. Contact of blood with artificial surfaces of the extracorporeal circuit of RRTs triggers several plasmatic pathways and activation of platelets and leucocytes [74]. Of the total surface area available for these interactions between blood and materials, the membrane within the dialyser constitutes the largest stimulus. The choice of the base polymer is believed to be the decisive factor determining the extent to which blood components are activated. However, it is not the only criterion, as the properties of the final product define the interaction between blood and artificial surfaces. The type of copolymer and solvent used in the spinning of the fibres and the diverse spinning conditions determine the physiochemical properties of the blood-contacting surface. The degree of surface hydrophobicity–hydrophilicity, surface charge and tension as well as surface chemistry (available chemical groups) and roughness are all peculiar to each dialysis membrane's response toward affecting alterations of blood components [75, 76]. These are discussed in detail in the article on blood-compatibility in this supplement.

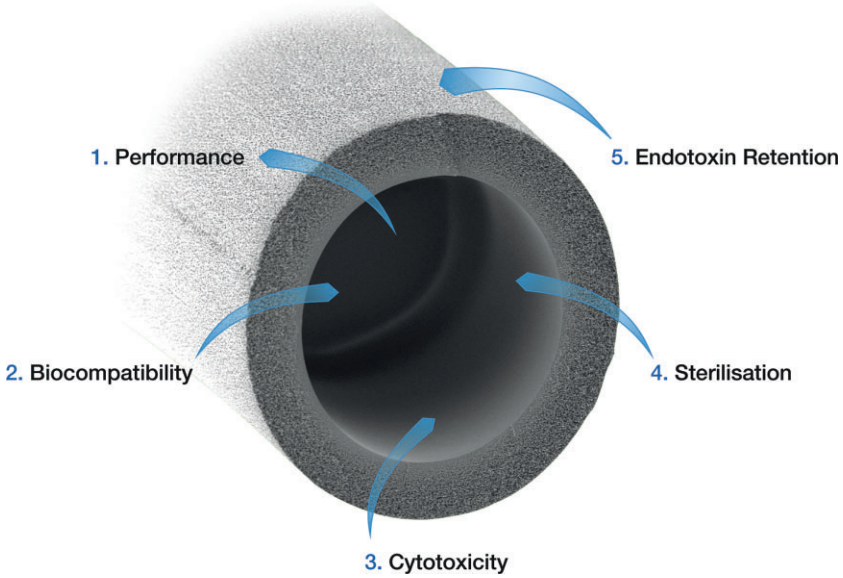

FIGURE 8: Criteria that collectively constitute the ideal modern dialysis membrane. Achieving the optimal balance for all these essential requirements is challenging and depends on the selection of the polymer systems, conditions of the ternary phase separation processes, thermodynamic conditions used for the spinning as well as subsequent handling steps involved in the entire manufacturing processes. 1. Performance: high removal rates of fluid and a broad spectrum of small and large uraemic toxins—without inadvertent loss of albumin that highly open membranes cause. 2. Biocompatibility: limiting the effects of unavoidable interactions between blood/artificial surfaces of the extracorporeal circuit. 3. Cytotoxicity: prevention of leaching of substances from the membrane (and other extracorporeal circuit components) and entering tissues, causing cell reactions. 4. Sterilisation: as utmost safety for patients must be ensured during each treatment session, efficient sterilisation procedures are required without changing membrane characteristics. 5. Endotoxin retention: as dialysis fluids could potentially be contaminated with bacterial endotoxins, causing persistent low-grade inflammation, modern dialysis membranes need to have high endotoxin retention capabilities.

Impact of outer fibre wall chemistry on safety: endotoxins. Transport across dialysis membranes is bidirectional, i.e. not only from the blood compartment (fibre lumen) to the dialysis fluid compartment but also vice versa. Dialysis fluid solutions contain some electrolytes and a bicarbonate buffering system and glucose to replenish plasma with substances that are removed inadvertently during the dialysis process. During this transport from dialysis fluid to the blood compartment, substances other than those intended may enter the patient's bloodstream. Dialysis fluids may be contaminated with bacteria, as their proliferation is aided by the fluid's constituents, e.g. bicarbonate [77]. As by-products of bacterial growth and death (lysis), endotoxins of different sizes and biological potency may enter the bloodstream (by diffusion or backfiltration, or during direct infusion of substitution fluid prepared from dialysis fluids into the blood circuit in convective treatment modalities like haemodiafiltration) and elicit adverse reactions that in extreme case could be life threatening [78, 79].

A prerequisite of modern dialysis membranes is their capacity to prevent the transfer of endotoxins to the patient should dialysis fluid purity measures fail, allowing bacterial growth [80]. The removal of endotoxins is achieved mainly by the mechanism of adsorption, whereby certain chemical entities of the endotoxins [lipopolysaccharides (LPS)] interact with appropriate domains of the polymers used in the manufacture of the membranes [81, 82]. The interaction of hydrophobic domains of LPS and hydrophobic regions of polysulfone polymer has been utilised to develop special filters to enhance the microbiological safety of fluids for all dialysis therapies [83–85]. Thus the type and composition of the polymer(s) impart a surface chemistry at the outer wall of membranes that has repercussions for the safety of dialysis procedures, particularly for convective dialysis therapies [55].

CRITERIA CONSTITUTING THE 'IDEAL' MODERN DIALYSIS MEMBRANE: IMPACT ON PATIENT OUTCOMES

From the sections above, it is apparent that the materials and conditions selected for the manufacture of hollow fibre membranes have an impact far beyond the central function of elimination of uraemic toxins during HD. As the HD procedure entails prolonged and repeated contact of flowing blood with an extracorporeal circuit having different artificial surfaces and geometries, several supplementary issues arise and need to be addressed when developing dialysis membranes [52, 61, 86]. In achieving the detoxification function, the patient should not be exposed to inadvertent reactions that either compromise his/her safety or affect the proper functioning of the device. A list of the ideal criteria of modern dialysis membranes has been proposed and has to be taken into account by all membrane manufacturers (shown in Figure 8) [61]. Efficient removal of uraemic toxins (detoxification) may be the primary focus, but other issues shown in Figure 8 are of equal significance in determining the impact of the dialysis membrane on the long-term outcomes of patients [55, 87–92].

Persistent, low-grade inflammation is now recognised as a hallmark feature of CKD, being involved in the development of all-cause mortality in these patients [93, 94]. Further, with the strong relationships between inflammation, malnutrition and atherosclerosis—all of which contribute to the high cardiovascular complications most HD patients suffer from—restricting inflammation is considered a core objective of dialytic therapies [95–97]. As the dialysis procedure itself has the potential to add to this inflammatory insult, dialysis modalities, treatment parameters and judicious selection of components of the therapy can all help alleviate this burden [90, 98–100]. We have

shown that the selection of appropriate membranes used for patients can help mitigate the pro-inflammatory stimuli that arise during each treatment session. Having membranes that are able to adsorb bacterial fragments and LPS from potentially contaminated dialysis fluid or those that are more biocompatible, particularly in terms of reduced activation of complement and leucocytes, helps curtail activation of inflammatory pathways [81, 101–103].

To conclude, membranes for HD have evolved and improved beyond measure from the experimental membranes available in the early developmental phases of dialysis. Today, the key functional determinants of dialysis membranes have been identified both in terms of their potential to remove uraemic toxins as well the subsidiary criteria they must fulfill to avoid undesirable patient reactions and to ensure safety. The production of hundreds of millions of kilometres of hollow fibre membranes is truly a technological achievement to marvel, particularly in ensuring that the fibre dimensions of wall thickness and inner lumen diameter and controlled porosity—all so vital to the core solute removal function—are maintained for every centimetre of the fragile fibres. With CKD now on the increase as one of major non-communicable diseases, production of membranes will increase in parallel with the increase in the number of patients expected to require HD therapies [41, 104, 105]. With increasing cost constraints in healthcare and environmental awareness, the challenges for producers of dialysis membranes in the future are enormous, as quality cannot in any way be compromised for the life-sustaining—like the natural membranes within all living organisms—function artificial dialysis membranes serve.

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