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EDITORIAL REVIEW

Clinical implications of hemodialysis membrane biocompatibility

For more than 250,000 patients worldwide, hemodialysis is a life-sustaining procedure; it is also associated with acute side-effects that may be life-threatening and chronic side-effects that diminish their quality of life. Many of these complications are associated with the diffusive and convective components of hemodialysis, that is, the rate of change of osmolarity and the rate of ultrafiltration. However, in recent years, it has become clear that hemodialysis can no longer be considered a simple process whereby blood and dialysate are separated by an inert semi-permeable membrane. Significant side-effects may occur from the interactions of blood with various components of the hemodialysis equipment [1–3].

Biocompatibility, as it relates to hemodialysis, can be defined as the sum of specific interactions between blood and the artificial materials of the hemodialysis circuit. Because the components of the hemodialysis procedure are "foreign," that is, non-self, the interaction of blood with these components is best described as an "inflammatory response." When this response is mild and well tolerated, the material can be termed biocompatible. When it is intense, it may adversely affect patient well-being or lead to deleterious outcomes. Importantly, in the chronic hemodialysis patient these interactions are repetitive and occur three times a week. Therefore, even mild interactions may, on a chronic basis, lead to adverse clinical sequelae.

There are other aspects of the biocompatibility of the hemodialysis procedure, including the biocompatibility of the dialysate (sodium concentration, acetate/bicarbonate, etc.), of the dialytic procedure (intermittent, continuous, sequential), and of the other components of hemodialysis (blood lines, blood access). Finally, the initial sterilant (ethylene oxide, steam or gamma rays), reuse procedure (manual, automated), and sterilant (formaldehyde, hypochlorite, peracetic acid/hydrogen peroxide), as well as residual materials from the manufacturing process (leachable phthalate), represent other aspects of biocompatibility of the hemodialysis procedure. However, in this review the known interactions between blood and the new hemodialysis membranes will be emphasized, with only limited attention to the effect of reuse on these interactions.

Historically, cellulose-based materials were used for the manufacturing of hemodialysis membranes and remain to date the most commonly used membranes. Such a membrane can be prepared by dissolution of purified cellulose (usually cotton fibers) in an ammonia solution of cupric oxide, resulting in Cuprophane®. Various modifications to this repeating polysaccharide structure of cellulosic membranes are available. These alterations have resulted in relatively minor changes in the characteristics of the membrane, for example, cellulose acetate membrane, in which the polysaccharide structure is modified by replacement of hydroxyl ions with acetate radicals. In addition, several synthetic materials have been brought to clinical practice and, in general, are distinguished by a decrease in the intensity and specificity of the blood membrane interactions (Table 1).

The synthetic polymers can be grouped as either hydrophilic or hydrophobic [4]. In general, the hydrophobic membranes are apolar, have low energy of interactions with water, adsorb proteins, are more porous and have high ultrafiltration coefficients. This category of hydrophobic membranes includes the polysulfone (PS), the polymethylmethacrylate (PMMA) and the polyacrylonitrile (PAN) membranes [5]. Indeed, the ability of these membranes to adsorb proteins may be a determinant of their biocompatibility, since membranes such as PAN activate the complement system readily, but have such a high adsorptive capacity for complement activation products that the net effect is only a modest elevation of these products systemically [6].

Activated pathways

During contact of blood with the hemodialysis membrane, several homeostatic reactions are activated. These include the complement cascade, the coagulation cascade and the interrelated contact-phase reaction. In addition to these protein-mediated pathways, increasing evidence suggests that cellular mechanisms can also be activated during hemodialysis, both upon direct contact of cells with the membrane [7], as well as byproducts of activation of the humoral pathways, such as complement activation products. Recent work has documented the activation of neutrophils, leading to the up-regulation of adhesion receptors [8, 9], release of proteinases and other intracellular enzymes, reactive oxygen species [10], leukotrienes [11] and platelet activating factor (PAF), as well as the activation of monocytes leading to the production of monokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) [12–14], and activation of platelets leading to the release of thromboxane B2 [15–17]. As shown in Figure 1, in many instances these pathways are interrelated and the participation of one leads to the participation of the other.

The details of activation of these reactions and their enzymatic and non-enzymatic control is beyond the scope of this review. Instead, these reactions will be discussed in terms of their known and potential links to clinical sequelae that have been described in the hemodialysis patient.

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Table 1. Types of hemodialysis membranes

Membrane type	Membrane structure
Cellulosic	
Cellulose	Polysaccharide units with hydroxyl groups formed from cotton fibers
Derivatized cellulosic	
Cellulose acetate	Cellulose with 4 out of 5 hydroxyl groups replaced with acetate
Hemophane	Cellulose with 1.5% hydroxyl groups replaced by diethylaminoethyl radicals
Synthetic polymers	
Polyetherpolycarbonate	Hydrophilic synthetic
Ethylvinyl alcohol	Hydrophilic synthetic
Polysulfone (PS)	Hydrophobic synthetic
Polyamide	Hydrophobic synthetic
Polymethylmethacrylate (PMMA)	Hydrophobic synthetic
Polyacrylonitrile (PAN)	Hydrophobic synthetic

Acute sequelae of bioincompatibility

Complement activation

Although a profound, but transient, neutropenia during hemodialysis was initially observed in 1968, its cause remained unknown until Craddock's elegant work documenting neutropenia and hypoxemia following injection of plasma that had been exposed to cellulosic membrane into rabbits [18, 19]. Detection of products of complement activation of the common pathway, without evidence of pronounced activation of the classical pathway, have confirmed that complement activation during hemodialysis occurs via the alternative pathway. The extent of complement activation depends on the type of membrane used. In general, cellulose-derived membranes result in a much more profound activation of complement than non-cellulosic membranes.

Much research has been devoted to the determinations of surface structures or moieties that govern the activation of complement by biomaterials [20, 21]. The propensity of cellulosic membranes to activate complement is probably related to the polysaccharide structure of cellulose, and specifically to the hydroxyl groups contained in this structure. More recently, the inhibitory role of factor H of the alternative complement pathway has been emphasized. Thus, a membrane that promotes preferential binding of Factor H and does not favor the binding of factor B has a low capacity to activate complement [22].

The activation of complement is maximum at 15 minutes but lasts up to at least 90 minutes, following initiation of hemodialysis with new cellulose-derived membranes [23]. As hemodialysis proceeds, the rate of complement activation decreases, as suggested by the difference between the simultaneously drawn efferent and afferent samples across the dialyzer [23]. The mechanisms of passivation of these surfaces after initiation of hemodialysis have not been well defined, but probably include specific deposition of complement fragments such as C3b or C1q, as well as nonspecific deposition of fibrin on the activating sites of the hemodialysis membrane [22].

Products of complement activation such as C3a and C5a are potent, biologically active agents capable of producing intense vascular smooth muscle contraction, and in several animal models can induce anaphylaxis, hence the term "anaphylatoxin" (Table 2). The spasmogenic effect of the anaphylatoxins on smooth muscle cells is dose-related and the sensitivity of different species to it is variable [24]. Animals exposed to blood in contact with complement activating dialysis membranes developed electrocardiographic changes consistent with ischemia, acute elevations of pulmonary artery pressure and acute reduction of cardiac output, as well as increased vascular permeability and release of histamine from mast cells [25]. Similar acute hemodynamic changes, both in the systemic and pulmonary circulations, are also seen in animals infused with C5a, suggesting that C5a is the putative factor in such reactions [26].

The clinical relevance of anaphylatoxin release can be ascertained from symptoms that are described in a number of patients during their exposure to a new cellulosic dialyzer. A number of double-blind studies have shown a marked difference in the incidence of adverse symptoms, particularly chest pain, back pain and shortness of breath, between new cellulosic membranes that activate complement vigorously and reprocessed membranes that have a significantly attenuated ability to activate complement [27–32]. In a prospective study, we also showed that a subset of patients who consistently developed chest pain, back pain and shortness of breath during the first few minutes of hemodialysis, appeared to activate the complement pathway more vigorously (or clear the anaphylatoxin products more slowly). In any case, these patients had levels of C3a and C5a, which were several-fold higher than other patients dialyzed with the same membrane surface [33]. This difference in the level of anaphylatoxins is likely to be the explanation for the "First-Use Syndrome" which affects 5 to 10% of patients receiving hemodialysis with new cellulosic membranes, particularly ones with large surface areas and hence, a greater propensity to activate complement [34]. Whether these anaphylatoxins act directly by themselves or via their action on mast cells and liberation of histamine is not clear at present. It must be stressed that these symptoms, which are directly attributable to the extent of complement activation [35], are separate from the reactions that have characterized some of the more dramatic reports of anaphylactic-type reactions and which have been found to be due to ethylene oxide antigenicity [36–38].

Contact pathway activation

The mechanism by which a surface induces contact pathway activation involves the binding of Hageman factor (Factor XII) and circulating complexes of high molecular weight kininogen (HMWK) with pre-kallikrein. Activation of Hageman factor and pre-kallikrein results in the formation of kallikrein at the surface and is subject to regulation by several plasma inhibitors, such as α_2-macroglobulin [39]. This pathway is more easily activated by negatively charged surfaces, because the first step in the activation depends on the charge-induced conformational changes in Factor XII or Hageman factor. This conformational change allows reciprocal activation of kallikrein and Hageman factor. Once activated, kallikrein is also potent in liberating kinins from HMWK as shown in Figure 1. As expected, the extent of activation of this pathway is generally related to the extent of negative surface charge on a membrane. A recent study has investigated the surface charges of hemodialysis membranes and found that whereas the Cuprophane® membrane has a neutral charge, the polyacrylonitrile (PAN) membrane has a high negative charge (Table 3) [39, 40]. This

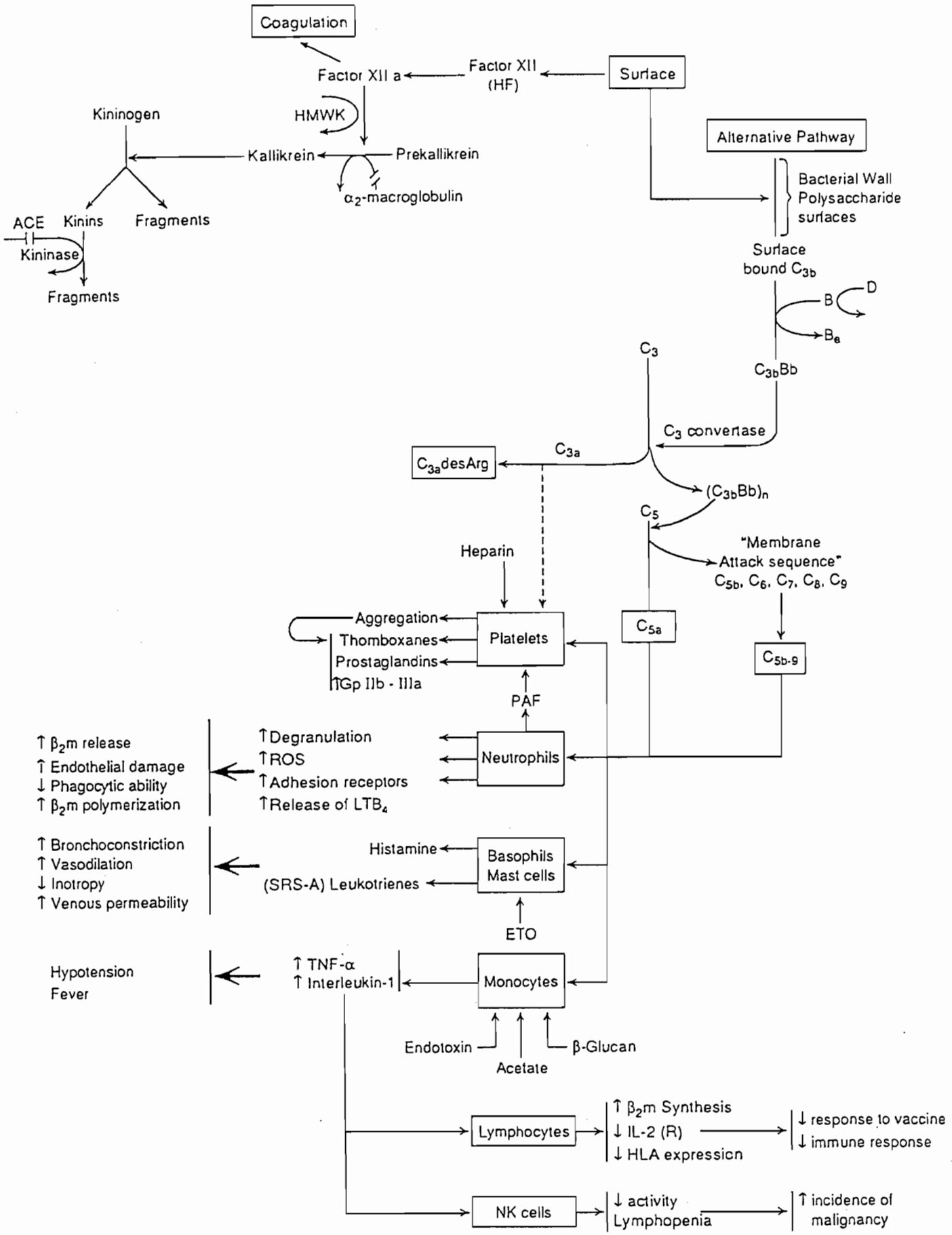

Fig. 1. *Schematic diagram of multiple pathways involved in blood-membrane interactions.*

Table 2. Sequelae of complement activation (alternative pathway)

1. Release of anaphylatoxins (C3a, C5a) leading to:
Smooth muscle contraction
Increased vascular permeability
Release of histamine from mast cells
2. Formation of membrane attack complex (C5b-9)
3. Activation of neutrophils
—Degranulation and release of granulocyte enzymes (such as, proteases)
—Production of reactive oxygen species (ROS)
—Increased expression of adhesion receptors
—Enhanced arachidonic acid metabolism (LTB_4) and PAF
4. Activation of monocytes
—Increased transcription of IL-1β and TNF-α

Table 3. Surface potential of hemodialysis membrane[a]

Membrane	Charge
Cuprophane®	−0
Cellulose acetate	−3.4
Polyacrylonitrile	−153.9

[a] Methylene blue dye method

difference in negative surface charge correlated with the degree of Hageman factor, kallikrein activation and early bradykinin generation.

Bradykinin is a potent vasoactive agent and is quickly degraded by the kininase enzymes. The clinical consequences of contact pathway activation are generally limited in consequence, except in hemodialysis membranes that have very high negative surface charges, such as the PAN membrane, and particularly in patients who may be on angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors not only block the angiotensin-converting enzyme, but also the kininase enzyme [41]. Therefore, in the presence of ACE inhibitors, bradykinin is not degraded and a large concentration may remain in the circulation, and severe anaphylactic reactions consisting of cardiovascular collapse may result. Indeed, anaphylactic reactions have been reported in several studies of patients dialyzed with the AN69 polyacrylonitrile membrane who are simultaneously on ACE inhibitors [42, 43]. A recent report showed that of 72 patients on a combination of ACE inhibitors and the PAN (AN-69) membrane, 41 developed anaphylactic reactions, whereas none of the 71 patients taking ACE inhibitors, but dialyzed with other membranes, and only 2 of 519 patients (0.4%) dialyzed with PAN membrane, but not on ACE inhibitors, developed anaphylactic reactions [43]. Recent work by Lemke and Fink, has shown that in the presence of ACE inhibitors, large amounts of bradykinin are generated in a dose-dependent manner when blood is in contact with the PAN (AN-69) membrane, but not the Cuprophane® membrane [44]. Thus, the variability in the incidence of anaphylactic reactions may reflect different systemic concentrations of the ACE inhibitors and bradykinin levels. More recently, such reactions have been reported in patients on ACE inhibitors and dialyzed with polysulfone and cellulose acetate membranes that have been reused with Renalin® [45]. At present, there are no data on the surface charges of these membranes or whether these reactions are related to the membrane or sterilant-membrane interaction.

Chronic sequelae of bioincompatibility

Amyloid bone disease

Amyloid fibrils, consisting of β_2-microglobulin (β_2m) polymers have been recognized as a pathologic process in long-term hemodialysis patients since 1983. This amyloidosis, designated Aβ_2m, is associated with a constellation of signs and symptoms, including carpal tunnel syndrome, diffuse arthropathy, lytic bone lesions, pathologic fractures with soft tissue swelling and tendinitis. Aβ_2m is a cause of significant morbidity in the long-term hemodialysis patient. Although amyloid bone disease has been reported in a few patients before institution of hemodialysis [46, 47], and in a few long-term peritoneal dialysis patients [48], there is increasing evidence that the bioincompatibility of hemodialysis membranes may participate in the development of this disease process [49–51]. There have been several recent studies of large populations that have documented a higher incidence of amyloid bone disease in patients chronically dialyzed with cellulosic-type membranes. Although some studies showed an increase in the incidence of Aβ_2m in patients dialyzed with cellulosic membrane, but which were not statistically significant [52], others that were methodologically more rigorous have shown clear-cut statistical significance [53–57]. The best example is a study by van Ypersele and his group from Belgium, which clearly showed that the "survival without amyloid bone disease" is significantly shorter in patients dialyzed with Cuprophane® membrane than in patients dialyzed with the PAN membrane [53]. The difference in relative risk was clearly higher the older the patient; for example, a 60-year-old patient dialyzed with the Cuprophane® membrane had 10 times the risk of developing Aβ_2m disease compared to a similar patient on the PAN membrane [53]. It is possible that this risk is even higher if bone biopsies are available for diagnosis of Aβ_2m, since other studies showed an incidence of 20% in unselected bone biopsies in patients on hemodialysis with a Cuprophane® membrane for more than ten years [58].

The pathogenesis of the increased development of β_2m amyloid bone disease in patients dialyzing on cellulosic membranes is multifactorial (Table 4). β_2m is expressed on the surface of all nucleated cells; it is also released from intragranular stores by degranulating granulocytes, as occurs during hemodialysis with complement-activating membranes [59, 60]. In addition, several studies have shown that the contact of mononuclear cells with cellulosic membrane, as well as complement activation products C5a and C5b-9, leads to the increased transcription, synthesis and release of β_2m by these cells [61, 62]. Two *in vivo* studies, in which patients were prospectively dialyzed on biocompatible (PMMA) and bioincompatible (Cuprophane®) membranes showed a small (20%), but statistically significant increase in β_2m production by mononuclear cells when the patients were chronically dialyzed with the Cuprophane® membrane [63, 64]. Other studies, using ^{131}I-β_2m to study β_2m synthesis in different patient populations showed that patients dialyzed with Cuprophane® membrane had a β_2m synthesis rate that was 25% higher than in patients dialyzed with a biocompatible membrane, although this difference was not statistically significant, probably because of the small number of patients studied [65]. Using similar techniques, other studies using small numbers of different patient populations and with different levels of residual renal function, did not show as marked a

Table 4. Biocompatibility factors in the development of β_2m amyloid bone disease

A. Cellulosic membranes lead to an increase of synthesis and release of β_2m by MNC
B. Cellulosic membranes lead to the release of proteases (gelatinase, elastase) and ROS which favor polymerization of β_2m into amyloid.
C. Low flux cellulosic membranes do not adsorb or clear β_2m from the circulation.
D. Biocompatible membranes favor maintenance of residual renal function and endogenous β_2m excretion.

difference [66, 67]. Although serum β_2m levels may not increase appreciably during hemodialysis with cellulosic membranes, particularly if intradialytic changes in extracellular volumes are taken into account, it must be recalled that the additional synthesis induced by the bioincompatibility of the membrane is small compared to the high serum concentration of β_2m that results from loss of excretion by the native kidneys in patients with end-stage renal disease [67–69].

An additional factor in the propensity of patients dialyzed with cellulosic membranes to develop β_2m amyloid bone disease may be due to the fact that most of the cellulosic membranes are "low-flux" membranes; these membranes do not have pore sizes large enough or an adsorptive surface to effect a significant clearance of β_2m from the circulation. Because of these factors, patients dialyzed with biocompatible, high-flux membranes, have a pre-hemodialysis plasma β_2m level that is approximately 30% lower than patients dialyzed with the Cuprophane® membrane [70]. Thus, patients on Cuprophane® membrane are chronically exposed to a higher level of β_2m. More importantly however, is the fact that the activation of neutrophils by cellulosic membranes leads to the release of proteases, as well as reactive oxygen species, which may further enhance the polymerization of β_2m into amyloid fibrils. Indeed, analysis of the amino acid sequence of β_2m amyloid fibrils has revealed that these deposits consist of intact β_2m fibrils, as well as lysine-specific cleavage fragments of β_2m that represent limited proteolysis of β_2m by proteases, such as those released by activated neutrophils [71]. In preliminary work, we demonstrated that β_2m released by the spontaneous activation of endothelial cells in culture can be identified as a single band (at the 12 KD region) by gel electrophoresis, whereas β_2m released during contact with endothelial cells with C5a-activated-neutrophils had multiple bands, representing multimers of the intact β_2m molecule [72]. This suggests that a microenvironment of activated neutrophils, endothelial cells and complement fragments, such as exist in the pulmonary vasculature during hemodialysis with cellulosic membranes, may be conducive to the polymerization of β_2m [73]. Thus, it is likely that the relationship of hemodialysis with cellulosic membranes to the development of Aβ_2m bone disease is due to a combination of increased synthesis, lack of removal, and conditions that favor the polymerization of β_2m.

Incidence of infection

Despite many advances in the range of antimicrobial therapy and in the care of patients on chronic maintenance hemodialysis over the past two decades, there has been virtually no change in the incidence of life-threatening infection in hemodialysis-dependent patients. Many studies have shown that infections cause approximately 20% of all deaths in this patient population. A more recent study, using careful chart reviews, suggested that infection-related mortality is much higher and accounted for more than 36% of all deaths. Beyond six years of hemodialysis, infections were the most common cause of death in patients starting hemodialysis under the age of 60 years [74]. The majority of these infections are generally due to common catalase-producing bacteria rather than to opportunistic infections.

Although patients on chronic hemodialysis have multiple co-morbid conditions that predispose them to the development of infections (repetitive breaks of skin integrity during cannulation of fistula, malnutrition, etc.), there is increasing evidence that the hemodialysis membrane plays an important role in this enhanced susceptibility to infections.

The repetitive exposure of blood to bioincompatible cellulosic membranes leads to the recurrent activation of complement, degranulation of neutrophils and the release of reactive oxygen species [10, 23]. Although the reactive oxygen species are bactericidal, the unintended release of these molecules during hemodialysis with cellulosic membranes results in detrimental effects consistent with tissue injury [75], and importantly, in decreased responsiveness to further stimuli [76]; this refractoriness occurs particularly intradialytically when the skin integrity is violated and the patient is directly exposed to potentially non-sterile surfaces [10, 77, 78]. Chronic hemodialysis with the cellulosic membrane also leads to the attenuation of the ability of neutrophils harvested pre-hemodialysis to respond to phagocytic stimuli [76].

Almost all studies examining granulocyte chemotaxis, adherence and expression of receptors involved in phagocytosis have demonstrated substantial defects in patients dialyzed with the Cuprophane® membrane, even when compared to uremic patients prior to initiation of hemodialysis [76, 79, 80]. These defects in patients dialyzed with the cellulosic membrane are most prominent intradialytically. A recent study has also demonstrated a significant decrease in the expression of L-selectins on neutrophils harvested during hemodialysis; L-selectins are the receptors known to be involved in granulocyte-endothelial adhesion [81–83]. Indeed, endothelial cell adhesion has been shown to be significantly decreased when neutrophils are harvested during hemodialysis with the cellulosic membrane, but not when they are harvested from patients dialyzed with the PMMA membrane [81]. This defect may impact on the ability of neutrophils to extravasate through endothelial cells to sites of infection, and may thus play a role in the incidence of infections in hemodialysis patients.

Monocytes, which function as circulating macrophages and play a crucial role in antigen presentation and immune response, are also activated during hemodialysis with cellulosic membranes. Therefore, chronic exposure to these membranes also leads to their refractoriness of monocytes to further stimuli [10, 84, 85]. Several studies have documented defects in monocyte function in hemodialysis patients, such as defective Fc-receptor function [86] and monocyte-dependent IL-2 production by activated T cells [87, 88]. In an *in vitro* model of hemodialysis, monocyte function was found to be significantly decreased during exposure to cellulosic membranes [85].

Other studies have also pointed out specific defects in the cellular immunity of patients dialyzed on different membranes [89–92]. Recent studies from our laboratory have demonstrated that chronic hemodialysis with cellulosic membranes exacerbates the defect in T cell function in hemodialysis patients. By examining the expression of high-affinity IL-2 receptors, which are crucial in the immune response, we found that chronic exposure of patients to these bioincompatible membranes significantly attenuates the expression of high affinity IL-2 receptors on mononuclear cells. The change of dialyzer membrane to a more biocompatible surface, such as PMMA, improves the expression of these receptors and these patients have high affinity IL-2 receptors comparable to those found in normal controls [93]. Raij and Ray found decreased activity of natural killer (NK) cells in blood from normal volunteers exposed to different hemodialysis membranes [94, 95]. Our own studies have confirmed that in patients chronically hemodialyzed with bioincompatible membranes, there was a significant decrease in NK cytolytic activity against their classical target cells K562 [96]. Refractoriness to mitogen stimulation, decreased proliferative response, decreased IL-2 generation and the depressed mixed lymphocyte reactions have also been documented in patients hemodialyzed with the Cuprophane® membrane compared to patients dialyzed with biocompatible membranes [97–99].

The association of cellulosic membranes with a higher incidence of clinical infection in chronic hemodialysis patients is supported by retrospective studies which compared the major causes of mortality in approximately 1,000 patients before and after their hemodialysis membranes were changed from a cellulosic to a biocompatible membrane [100]. The most significant difference in the cause of death between these two periods of time was in the incidence of infection, which was decreased by approximately one-half during the period they were dialyzed with the biocompatible polysulfone membrane. These dramatic results were confirmed by another study, in which the rate of hospitalization for infections in patients switched to a PS membrane was half the rate of hospitalization for infections in patients dialyzed with the Cuprophane® membrane [101]. In another study, patients randomized to chronic hemodialysis with cellulosic membranes had a significantly attenuated metabolic response to phagocytic stimuli such as latex or zymosan, compared to neutrophils similarly harvested pre-hemodialysis from patients on the biocompatible polysulfone membrane [76]. Interestingly, during a follow-up of approximately six months, there was also higher incidence of clinical infections in the patients initiating hemodialysis on the Cuprophane® membrane, compared to those initiated on the polysulfone membrane; however, because of the small number of patients, the results had only marginal statistical significance.

Other studies have confirmed an improvement in the lymphopenia in patients on chronic hemodialysis once their hemodialysis membrane was changed to a biocompatible high-flux membrane [97]. Nevertheless, studies to document changes in clinical cellular immunity (such as, specific antibody formation in response to vaccines) as a function of hemodialysis with membranes of different biocompatibilities have not been published [87, 102].

Resolution of acute renal failure

The suggestion that the dialytic procedure itself may impact on the rate of recovery from acute renal failure (ARF) was first put forward by Solez et al and Conger et al [103, 104]. They examined the histology of renal tissue obtained from wounded soldiers who developed ARF and required hemodialysis for a prolonged period of time. They commented on the presence of fresh areas of tubular necrosis, even though the initial injury was remote. These observations confirmed comments by several clinical nephrologists that the institution of hemodialysis in patients with ARF, who may have modest residual renal function, often causes cessation of urine flow and further loss of residual renal function once hemodialysis is initiated. It was postulated that loss of autoregulation of renal perfusion combined with episodes of hypotension during hemodialysis results in new areas of ischemia in the kidney [105].

Other investigators have pointed out the adverse role that infiltrating leukocytes can play in the recovery of ARF in several experimental models of obstruction and nephrotoxic serum nephritis [106, 107]. More recently, Linas and his colleagues have shown that the adverse effects of activated neutrophils are particularly evident on an ischemic kidney [108]. Thus, when isolated kidneys were made mildly ischemic and exposed to activated neutrophils, the GFR was considerably reduced. However, this did not occur when the isolated kidneys were exposed to non-activated neutrophils.

Our own previous work using a rat model with reversible ARF showed that the extent of recovery of ARF in animals exposed to stimuli that activated complement and granulocytes, such as the cellulosic hemodialysis membrane, is considerably less and slower than in animals with the same degree of renal failure exposed to a biocompatible (PAN) membrane [109]. The delayed recovery in the group of animals exposed to Cuprophane® was also associated with the presence of increased numbers of activated neutrophils in the renal parenchyma. Following this lead, a recent abstract outlined the preliminary results of a clinical study in which patients with all forms of ARF requiring hemodialysis were sequentially randomized to dialyze with either Cuprophane® membrane or the biocompatible low-flux PMMA membrane. These results suggest a statistically significant improvement in patient mortality and in the recovery of renal function in patients dialyzed with a biocompatible membrane compared to the group of patients dialyzed with the Cuprophane® membrane. Equally important, in patients who recover, the recovery occurred earlier in the group of patients dialyzed with the biocompatible membrane [110]. If confirmed, the clinical implications of these findings in terms of patient survival and hospitalization costs are quite important.

Catabolic effects of bioincompatibility

Several reports have documented the prevalence of malnutrition, as well as the adverse effects of this malnutrition on morbidity and mortality of the hemodialysis patient [111]. Malnutrition often occurs with protein intakes well above the minimum required for normal controls, suggesting a catabolic process in the hemodialysis-dependent patients. Indeed, patients on hemodialysis appear to have an accelerated catabolic process, which is particularly evident on hemodialysis days.

An important and emerging factor in this catabolic process is the hemodialysis membrane, an area that has been highlighted by several recent studies. Those by Bergstrom, Alvestrand and colleagues in Sweden, clearly point to a net protein catabolism when normal subjects were exposed (not dialyzed) to cellulosic membranes, but not when exposed to the PS or PAN (AN-69) membrane [112, 113]. By measuring net release of specific and total amino acids, they calculated that a 150 minute exposure to the Cuprophane® membrane resulted in a net degradation of approximately 15 to 20 g of muscle protein [112]. It is perhaps worthwhile to point out that in these studies the net release of amino acids observed was not during the exposure to the membrane, that is, during the first 150 minutes, but was seen approximately six hours after the start of hemodialysis and three hours after the end of hemodialysis. In a few subjects where the observations were continued, the amino acid release continued for up to nine hours after the start of hemodialysis [112]. It is therefore important that studies of the effect of the biocompatibility of hemodialysis membranes on the protein catabolic rate, and the possible effects of monocyte activation and cytokine release, be extended to the time frame in which these cytokines are known to cause an effect. Indeed, these observations are in line with the known time frame of monocyte activation, release of cytokines and their subsequent action on muscle cells [7, 14, 114].

These experimental studies are also supported by the observations of Lindsay that the relationship between the dose of hemodialysis (K_t/V) and the protein intake (reflected by the protein catabolic rate) was different for different membranes. Patients dialyzed on biocompatible membranes may have a better protein intake than patients dialyzed with a non-biocompatible membrane [115]. These observations are clearly in need of further confirmation by prospective clinical studies, but the evidence so far supports the hypothesis that the biocompatibility of the dialzyer membrane plays a substantial role in the catabolic process associated with hemodialysis, and may be a factor in the prevalence of malnutrition in the hemodialysis patient [111, 113].

Morbidity and mortality of hemodialysis patients

There are, at present, no randomized studies to judge the effects of biocompatibility of hemodialysis membrane on the serious morbidity (that is, hospitalization) and mortality of hemodialysis patients. However, two non-randomized studies support the possibility that the use of biocompatible membranes is associated with improvement in morbidity and mortality when compared to patients dialyzed with the cellulosic membrane.

Chanard et al, studied the morbidity of hemodialysis in two groups of patients comparable in age, the major factor determining morbidity and mortality [116]. One group of 31 patients was dialyzed with a Cuprophane® membrane and their morbidity was compared with another group of 31 patients dialyzed with the PAN membrane over approximately 9,000 hemodialysis sessions. The number of hospitalizations was significantly higher for the Cuprophane® group (6.0 ± 1.1 days/patient/year) than for the PAN membrane group (2.1 ± 0.5 days/patient/year).

A more recent study compared the survival of patients who were switched from hemodialysis with a Cuprophane® membrane to hemodialysis with a high-flux biocompatible (PS) membrane [101]. Of the 80 patients who died during the study period, 69 were receiving conventional hemodialysis with cellulosic membranes and 11 were receiving hemodialysis with the high-flux, biocompatible polysulfone membrane. Multivariate analysis, adjusted for all known comorbid conditions, showed that annual mortality was substantially less for patients treated with the biocompatible high-flux membrane, compared with that for patients treated with conventional hemodialysis (7% vs. 20%, $P < 0.001$). Although in the study there was no difference in the overall rate of hospital admissions, the infection-related admissions were twice as high for the cellulosic group than for the high-flux, bicompatible membrane group.

Finally, preliminary analysis by Lowerie of more than 340 dialysis facilities in the National Medical Care system showed that the average standardized mortality ration (SMR) for facilities using high-flux polysulfone membranes was 0.72 compared to patients in dialysis units utilizing cuprophane membrane. ($P < 0.005$) [117, 118].

As discussed earlier, the PS membrane differs from the cellulosic membranes, not only in its biocompatibility but also in terms of its high-flux capability, clearance of middle molecules, and generally larger surface areas that allows for greater reduction of urea per unit of time. The relative importance of any of these factors in the improvement of mortality cannot be clearly ascertained from these studies. While there are only limited data to support the influence of middle molecules on these outcomes [77, 119], there are data to support an influence of urea reduction on mortality [120]. Indeed, the preliminary analysis by Lowrie indicates that adjustment for urea reduction, using unequilibrated post-dialysis urea levels, attenuates the differences in average SMR. Nevertheless, units that use polysulfone membranes still had a lower average SMR (0.83 compared to units utilizing cellulosic membranes, P = NS) [118].

In the context of the previous disussion on the consequences of biocompatibility on neutrophil, monocyte and lymphocyte activation, it is likely that the biocompatibility characteristics of the high-flux membrane play an important role in the differences of mortality shown by these three independent studies.

Potential sequelae of bioincompatibility

The evidence for the sequelae of bioincompatibility of the hemodialysis membrane in the specific areas discussed above is supportive, but perhaps not conclusive. There are other areas in which membrane bioincompatibility may play a role, but the available evidence is either based primarily on animal data or *in vitro* work. Nevertheless, it is worthwhile to mention those areas as potential areas for further investigation.

Residual renal function

Clinical observations have long confirmed the possibility that initiation of hemodialysis is associated with a rapid decrease in the residual renal function of patients with chronic renal disease; patients who have managed to maintain a low GFR of around 10 ml/minute for several months, lose it very quickly once they are started on hemodialysis. The rate of decline of residual renal function is twice as fast in patients starting hemodialysis than in patients starting peritoneal dialysis [121]. Although there are no prospective clinical trials that have

confirmed the possible influence of bioincompatibility or the use of cellulosic membranes on the rate of decline of residual renal function, recent studies on animals with remnant kidneys (5/6 nephrectomies) suggest that such repetitive exposure may play a role. In groups of animals exposed (but not dialyzed) to the Cuprophane® membrane, there is a faster decline of residual renal function than in identical groups exposed to the PAN membrane [122].

The pathophysiology of these observations in patients and in the animal model has not been elucidated. However, it is likely that they are related to the extent of complement activation by different hemodialysis membranes. Although the activation of complement has been linked predominantly to the generation of anaphylatoxins such as C3a and C5a, recent evidence suggests that the subsequent generation of the terminal membrane attack complex (MAC), C5b-9 may also be a clinically important consequence of complement activation [123, 124]. A number of studies have clearly shown that the MAC is important in the development and propagation of several models of experimental glomerulonephritis [125]. Thus, the chronic activation of complement resulting in the generation of C5b-9 during hemodialysis with cellulosic membranes may well be involved in the more rapid decline of residual renal function in patients initiating hemodialysis. Clinical studies to document these differences in patients initiating hemodialysis with different membranes are ongoing.

Pulmonary changes

The recurrent contact of activated neutrophils and pulmonary endothelium during hemodialysis with cellulosic membranes has been discussed as a potential mechanism that favors the development of β_2m amyloid bone disease (see above). A specific protease that is released by activated granulocytes is elastase [126]. Preliminary experiments in our laboratory have confirmed that in patients dialyzed with cellulosic membranes, there is a large increase in the concentration of elastin fragments, most likely from the lung parenchyma. Although these proteases are inactivated by several inhibitory proteins (α_2-macroglobulin), there is evidence that the inhibitory proteins function less well in the presence of reactive oxygen species. It is possible, therefore, that patients chronically dialyzed with cellulosic membranes undergo chronic breakdown of their pulmonary elastin fibrils and have a higher propensity for the development of emphysematous changes than patients dialyzed with biocompatible membranes [127–129]. Such a study, however, has not been done.

Dialysis associated hypoxemia is multifactorial; the major determinant is hypoventilation seen with acetate dialysate and changes in respiratory quotient. However, in well-designed trails, DeBroe [29] and others [130] showed an important contribution from membrane bioincompatibility manifested as leukopenia.

RBC survival

Red blood cells act as major site for deposition of C5b-9, the membrane attack complex. The presence of protein S in plasma and two membrane proteins [homologous restriction factor (HRF) and membrane inhibitor of reaction lysis (MIRL)] act to attenuate the attachment of MAC on cells [131, 132]. However, once C5b-9 is deposited, it leads to the lysis of host cells by insertion of MAC into the membrane and by forming a lesion that results in a lethal or sublethal damage to the cell.

The potential clinical relevance of MAC would be evident in the determination of RBC half-life in patients dialyzed with different membranes. This has not been examined in well-controlled studies, but preliminary experiments in our laboratory suggest an increase in RBC osmotic fragility in patients dialyzed with Cuprophane® membrane, in contrast to the same patients dialyzed with a biocompatible membrane. Studies to define the RBC half-life or the sensitivity to similar doses of erythropoietin of patients dialyzed on different membranes have not been performed so far.

Conclusions

The biocompatible hemodialysis membrane can be defined as one that elicits the least amount of inflammatory response in patients exposed to it. These inflammatory responses have clinical consequences that range from acute hemodynamic instability (as in the first use syndrome and the anaphylaxis associated with the use of angiotensin-converting enzyme inhibitors and specific membranes) to the development of β_2m amyloid disease. An increased incidence of infections, slower recovery of function after acute renal failure, and improvement of morbidity and mortality may also be related to the biocompatibility characteristics of the hemodialysis membrane. Other potential consequences include the more rapid loss of residual renal function, development of emphysematous pulmonary changes consistent with loss of elastin from the lung and a decrease in RBC half-life. These actual and potential consequences of the hemodialysis membrane suggest that the biocompatibility of the membrane should be an important consideration in the prescription of hemodialysis.

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References

1. BASILE C, DRUEKE T: Dialysis membrane biocompatibility. *Nephron* 52:113–118, 1989
2. CHEUNG AK: Biocompatibility of hemodialysis membranes. *J Am Soc Nephrol* 1:150–161, 1983
3. VAN YPERSELE DE STRIHOU C, DEMEYER M: Are there long-term clinical consequences related to membrane biocompatibility? *Contrib Nephrol* 71:36–39, 1989
4. WINGARD RL, HAKIM RM: Dyspnea, back pain, and hypotension during a vacation hemodialysis, in, *Grand Rounds in Nephrology*, edited by STONE WJ, Boston, Mosby Year Book, 1992, pp. 155–167
5. LYMAN DJ: Membranes, in *Replacement of Renal Function by Dialysis*, edited by DRUKKER W, PARSONS FM, MAHER JF, Boston, Martinus Nijhoff, 1983, pp. 97–105
6. CHEUNG AK, CHENOWETH DE, OTSUKA D, HENDERSON LW: Compartmental distribution of complement activation products in artificial kidneys. *Kidney Int* 30:74–80, 1986
7. BETZ M, HAENSCH GM, RAUTERBERG EW, BOMMER J, RITZ E: Cuprammonium membranes stimulate interleukin 1 release and

arachidonic acid metabolism in monocytes in the absence of complement. *Kidney Int* 34:67–73, 1988
8. Arnout MA, Hakim RM, Todd RF, Dana N, Colten HR: Increased expression of an adhesion promoting surface glycoprotein in the granulocytopenia of hemodialysis. *N Engl J Med* 312:457–462, 1985
9. Castiglione A, Pagliaro P, Romagnoni M, Beccari M, Cavaliere G, Veneroni G: Flow cytometric analysis of leukocytes eluted from haemodialysis. *Nephrol Dial Transplant* 2:31–35, 1991
10. Himmelfarb J, Lazarus M, Hakim R: Reactive oxygen species production by monocytes and polymorphonuclear leukocytes during dialysis. *Am J Kidney Dis* 3:271–276, 1991
11. Strasser T, Schiffl H: Generation of leukotriene B4 by hemodialyzer membranes: A novel index of biocompatibility. *Klin Wochenschr* 69:808–812, 1991
12. Dinarello CA: Cytokines and biocompatibility. *Blood Purif* 8:208–213, 1990
13. Dinarello CA, Koch KM, Shaldon S: Interleukin-1 and its relevance in patients treated with hemodialysis. *Kidney Int* 33 (Suppl 24):21, 1985
14. Luger A, Kovarik J, Stummvoll HK, Urbanska A, Luger TA: Blood-membrane interaction in hemodialysis leads to increased cytokine production. *Kidney Int* 32:84–88, 1987
15. Hakim RM, Schafer AI: Hemodialysis associated platelet activation and thrombocytopenia. *Am J Med* 78:575–580, 1985
16. Himmelfarb J, Lazarus JM, Hakim RM: Increased expression of glycoprotein GP IIb/IIIa detected by flow cytometry on platelets during hemodialysis. *Kidney Int* (abstract) 31:234, 1987
17. Seyfert UT, Helmling E, Hauck W, Skroch D, Albert W: Comparison of blood biocompatibility during haemodialysis with cuprophane and polyacrylonitrile membranes. *Nephrol Dial Transplant* 6:428–434, 1991
18. Kaplow LS, Goffinet JA: Profound neutropenia during the early phase of hemodialysis. *JAMA* 203:1135–1137, 1968
19. Craddock PR, Fehr J, Delmasso AP, Brigham KL, Jacob HS: Hemodialysis leukopenia: Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. *J Clin Invest* 59:878–888, 1977
20. Chenoweth DE: Anaphylatoxin formation in extracorporeal circuits. *Complement* 3:152–165, 1986
21. Chenoweth DE, Cheung AK, Ward DM, Henderson LW: Anaphylatoxin formation during hemodialysis: Effects of different dialyzer membranes. *Kidney Int* 24:770–774, 1983
22. Cheung AK: Interactions between plasma proteins and hemodialysis membranes, in *Advances in Nephrology* (22nd ed), edited by Grunfeld JP, Back JF, Kreis H, Maxwell MH, Boston, Mosby Year Book, 1993, pp. 417–434
23. Hakim RM, Fearon DT, Lazarus JM: Biocompatibility of dialysis membranes: Effects of chronic complement activation. *Kidney Int* 26:194–210, 1984
24. Chenoweth DE: The properties of human C5a anaphylatoxin. *Contr Nephrol* 59:51–57, 1987
25. Walker JF, Lindsay RM, Peters SD, Sibbalb WJ, Linton AL: A sheep model to examine the cardiopulmonary manifestations of blood dialyzer interactions. *Am Soc Artif Int Organ* 6:123–130, 1983
26. Cheung AK, LeWinter MK, Chenoweth DE, Lew WYW, Henderson LW: Cardiopulmonary effects of cuprophane-activated plasma in swine. *Kidney Int* 29:799–806, 1986
27. Bok DV, Pascual L, Herberger C, Levin NW: Effect of multiple use of dialyzers on intradialytic symptoms. *Proc Clin Dial Transpl Forum* 10:92–98, 1980
28. Davenport A, Williams AJ: The effect of dialyzer reuse on peak expiratory flow rate. *Resp Med* 84:17–21, 1990
29. De Broe ME, Heyrman RM, De Backer WA, Verpooten GA, Vermeire PA: Pathogenesis of dialysis-induced hypoxemia: A short overview. *Kidney Int* 33 (Suppl 24):57, 1985
30. Kant KS, Pollak VE, Cathey M, Goetz D, Berlin R: Multiple use of dialyzers: Safety and efficacy. *Kidney Int* 19:728–738, 1981
31. Pollak VE, Charoenpanich R, Robson M, Kant KS: Dialyzer membranes: Syndromes associated with first use and effects of multiple use. *Kidney Int* 33 (Suppl 24):49, 1985
32. Robson MD, Charoenpanich R, Kant KS: Effect of first and subsequent use of hemodialyzers on patient well being. *Am J Nephrol* 6:101–106, 1986
33. Hakim RM, Breillatt J, Lazarus JM, Port FK: Complement activation and hypersensitivity reactions to dialysis membranes. *N Engl J Med* 311:878–882, 1984
34. Daugirdas JT, Ing TS: First-use reactions during hemodialysis: A definition of subtypes. *Kidney Int* 33 (Suppl 24):37, 1985
35. Jacob HS: Granulocyte-complement interaction. A beneficial antimicrobial mechanism that can cause disease. *Arch Intern Med* 138:461–463, 1978
36. Bommer J, Wilhelms OH, Barth HP, Schindela H, Ritz E: Anaphylactoid reactions in dialysis patients. Role of ethylene oxide. *Lancet* 21: 1985
37. Dolovich J, Marshall C, Smith E: Allergy to ethylene oxide in chronic hemodialysis patients. *Artif Organs* 8:334–337, 1984
38. Rockel A, Hertel J, Wahn U: Ethylene oxide and hypersensitivity reactions in patients on hemodialysis. *Kidney Int* 33 (Suppl 24):62, 1985
39. Schulman G. Hakim RM, Arias R, Silverberg M, Kaplan AP, Arbeit L: Bradykinin generation by dialysis membranes: Possible role in anaphylactic reaction. *J Am Soc Nephrol* 3:1563–1569, 1993
40. Thomaneck U, Vienken J, Waldschlager U: Detection of charges and their distribution on dialysis membranes with cationic/anionic dyes using confocal laser scanning microscopy. *Int J Artif Organ* 14:686–690, 1991
41. Zusman RM: Renin and non-renin mediated antihypertensive actions of converting enzyme inhibitors. *Kidney Int* 25:969–983, 1984
42. Tielmans C, Madhoun P, Lemars M, Schondere L, Goldman M, Vanherweghem JL: Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. *Kidney Int* 38:982–984, 1990
43. Parnes EL, Shapiro WB: Anaphylactoid reactions in hemodialysis patients treated with AN69 dialyzers. *Kidney Int* 40:1148–1152, 1991
44. Lemke HD, Fink E: Accumulation of bradykinin formed by the AN69- or PAN 17DX-membrane is due to the presence of an ACE-inhibitor *in vitro*. *J Am Soc Nephrol* (abstract) 3:376, 1992
45. Pegues DA, Beck-Sague CM, Woollen SW: Anaphylactoid reactions associated with reuse of hollow-fiber hemodialyzers and ACE inhibitors. *Kidney Int* 42:1232–1237, 1992
46. Zingraff JJ, Noel L-H, Bardin T, Atienza C: β_2m amyloidosis in chronic renal failure. *N Engl J Med* 323:1070–1071, 1990
47. Moriniere PH, Maire A, El Esper N: Destructive spondyloarthopathy with β_2m amyloid deposits in a uremic patient before chronic hemodialysis. *Nephron* 59:654–657, 1991
48. Gagnon RF, Noel H, van Ypersele de Strihou C: β_2m amyloidosis in a patient treated exclusively by CAPD. *Can Med Assoc J* 139:753–755, 1988
49. Stone WJ, Hakim RM: β_2m amyloidosis in long-term dialysis patients. *Am J Nephrol* 9:177–183, 1989
50. Drueke TB: β_2m amyloidosis and renal bone disease. *Miner Electrol Metab* 17:261–272, 1991
51. Fumitake G, Arakawa M: β_2m: Evidence for a new form of hemodialysis-associated amyloid protein. *Kidney Int* 33 (Suppl 24):30, 1985
52. Brunner FP, Brynger H, Ehrich JHH: Case control study on dialysis arthropathy: The influence of two different dialysis membranes: Data from the EDTA registry. *Nephrol Dial Transplant* 5:432–436, 1990
53. van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J: Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. *Kidney Int* 39:1012–1019, 1991
54. Miura Y, Ishiyama T, Inomata A: Radiolucent bone cysts and the type of dialysis membrane used in patients undergoing long-term hemodialysis. *Nephron* 60:268–273, 1992
55. Chanard J, Bindi P, Lavand S: Carpal tunnel syndrome and type of dialysis membrane. *Br J Med* 298:867–868, 1989

56. VANDENBROUCKE JM, HUAUX J-P, NOEL H: Capsulo-synovial and bone amyloidosis: Bicompatibility phenomenon of hemodialysis? *Kidney Int* 33 (Suppl 24):35–36, 1988
57. BOMMER J, SEELIG P, SEELIG R: Determinants of plasma biocompatibility. *Nephrol Dial Transplant* 2:22–25, 1987
58. ONISHI S, ANDRESS DL, MALONEY NA, COBURN JW, SHERRARD DJ: β_2m deposition in bone in chronic renal failure. *Kidney Int* 39:990–995, 1991
59. BJERRUM OW, BJERRUM OJ, BORREGAARD N: In neutrophils: An intragranular protein. *J Immunol* 138:3913–3917, 1987
60. PLESNER T, BJERRUM OJ: Distribution of free and HLA-associated human β_2m in some plasma membranes and biological fluids. *Scand J Immunol* 11:341–351, 1980
61. JAHN B, BETZ M, DEPPISCH R, JANSSEN O, HANSCH GM, RITZ E: Stimulation of β_2m synthesis in lymphocytes after exposure to cuprophane dialyzer membranes. *Kidney Int* 405:285–290, 1991
62. BETZ M, HUG F, BERNHARD J, DEPPISCH R, HANSCH GM, RITZ E: The cuprophane (Cu) induced stimulation of β_2m mRNA in mononuclear cells (MNC) is amplified by complement activation. *J Am Soc Nephrol* (abstract) 2:315, 1991
63. ZAOUI P, STONE WJ, HAKIM RM: Effects of dialysis membranes on β_2m production and cellular expression. *Kidney Int* 38:962–968, 1990
64. MEMOLI B, LIBETTA C, RAMPINO T: Hemodialysis related induction of interleukin-6 production by peripheral blood mononuclear cells. *Kidney Int* 42:320–326, 1992
65. FLOEGE J, BARTSCH A, SCHULZE M, SHALDON S, KOCH KM, SMEBY LC: Turnover of ^{131}I-β_2m in hemodialyzed patients. *J Lab Clin Med* 118:153–165, 1991
66. VINCENT C, CHANARD J, CAUDWELL V, LAVAUD S, WONG T, REVILLARD J-P: Kinetics of ^{125}I-β_2m turnover in dialyzed patients. *Kidney Int* 42:1434–1443, 1992
67. ODELL RA, SLOWIACZEK P, MORAN JE, SCHINDHELM K: β_2m kinetics in end-stage renal failure. *Kidney Int* 39:909–919, 1991
68. BERGSTROM J, WEHLE B: No change in corrected β_2m concentration after cuprophane haemodialysis. *Lancet* 1:628–629, 1987
69. HONIG A, MARSDEN T, SCHAD S, BARTH C, POLLOK M, BALDAMUS CA: Correlation of β_2m concentration changes to distribution volume. *Int J Artif Organs* 11:459–464, 1988
70. DIRAIMONDO CR, POLLAK VE: β_2m kinetics in maintenance hemodialysis: A comparison of conventional and high-flux dialyzers and the effects of dialyzer reuse. *Am J Kidney Dis* 5:390–395, 1989
71. LEMKE RP, HAMPLE H, LOBECH H: Lysine-specific cleavage of β_2m in amyloid deposits associated with hemodialysis. *Kidney Int* 36:675–681, 1989
72. ZAOUI P, HARRINGTON R, LEE W, HOOVER R, HAKIM R: Interaction of activated neutrophils with endothelial cells leads to increased generation of β_2m. *J Am Soc Nephrol* (abstract) 2:356, 1991
73. LINS RL, ZACHEE P, DAELEMANS R, BROECKE EV, BOOGAERTS MA, DEBROE ME: Red blood cell function and β_2m kinetics during cuprophane hemodialysis: A hypothesis. *Artif Kidney Dial* 12:638–641, 1989
74. MAILLOUX LU, BELLUCCI AG, WILKES BM: Mortality in dialysis patients: Analysis of the causes of death. *Am J Kidney Dis* 3:326–335, 1991
75. HALLIWELL B, GUTTERIDGE JMC, CROSS CE: Free radicals, antioxidants and human disease: Where are we now? *J Lab Clin Med* 119:598–620, 1992
76. VANHOLDER R, RINGOIR S, DHONDT A, HAKIM R: Phagocytosis in uremic and hemodialysis patients: A prospective and cross-sectional study. *Kidney Int* 39:320–327, 1991
77. VANHOLDER R, RINGOIR S: Infectious morbidity and defects of phagocytic function in end-stage renal disease: A review. *J Am Soc Nephrol* 3:1541–1554, 1993
78. HIMMELFARB J, AULT KA, HOLBROOK D, HAKIM RM, LEEBER DA: Intradialytic granulocyte reactive oxygen species production: A prospective, crossover trial. *J Am Soc Nephrol* (in press)
79. ILVENTO MC, DIEZ RA, ESTEVEZ ME, QUEVEDO A, ESTRAVIZ HO, SEN L: Hemodialysis decreases spontaneous migration of polymorphonuclears in chronic renal failure. *Dial Transplant* 21:705–708, 1992
80. DESCAMPS-LATSCHA B, HERBELIN A, NGUYEN AT, URENA P: Respective influence of uremia and hemodialysis on whole blood phagocyte oxidative metabolism, and circulating interleukin-1 and tumor necrosis factor. *Adv Exp Med Biol* 297:183–192, 1991
81. HIMMELFARB J, ZAOUI P, HOLBROOK D, HAKIM RM: Modulation of granulocyte LAM-1 and MAC-1 during dialysis—A prospective, randomized controlled trial. *Kidney Int* 41:388–395, 1992
82. TEDDER TF: Cell-surface receptor shedding: A means of regulating function. *Am J Respir Cell Mol Biol* 5:305–306, 1991
83. SPERTINI O, KANSAS GS, MUNRO JM, GRIFFIN JD, TEDDER TF: Regulation of leukocyte migration by activation of the leukocyte adhesion molecule-1 (LAM-1) selectin. *Nature* 349:691–694, 1991
84. BLUMENSTEIN M, ZIEGLER-HEITBROCK HWL, SCHILLER B, SCHMIDT B, WARD RA, GURLAND HJ: Differential activation of monocytes in haemodialysis patients exposed to different types of membranes. *Scand J Immunol* 31:183–190, 1990
85. ROCCATELLO D, MAZZUCCO G, COPPO R: Functional changes of monocytes due to dialysis membranes. *Kidney Int* 35:622–635, 1989
86. RUIZ P, GOMEZ F, SCHREIBER AD: Impaired function of macrophage Fc receptors in end stage renal disease. *N Engl J Med* 322:717–722, 1990
87. DUMANN H, MEUER S, MEUER ZUM BUSCHELFELDE KH, KOHLER H: Hepatitis B vaccination and interleukin-2 receptor expression in chronic renal failure. *Kidney Int* 38:1164–1168, 1990
88. MEUER SC, HAUER M, KURZ P, MEYER Z, BUSHENFELDE K, KOHLER H: Selective blockade of the antigen-receptor mediated pathway of T-cell activation in patients with impaired primary immune response. *J Clin Invest* 80:743–749, 1987
89. BEAURAIN G, NARET C, MARCON L: *In vivo* T-cell preactivation in chronic uremic hemodialyzed and non-hemodialyzed patients. *Kidney Int* 36:636–644, 1989
90. CHATENOUD L, DUGAS B, BEAURAIN G: Presence of preactivated T-cells in hemodialyzed patients: Their possible role in altered immunity. *Proc Natl Acad Sci USA* 83:7457–7461, 1986
91. STEFONI S, NANNI-COSTA A, BUSCAROLI A: Cellular immunology in regular dialysis: A biological model for biocompatibility evaluation. *Nephrol Dial Transplant* Suppl 2:4–9, 1991
92. CHATENOUD L, HERBELIN A, BEAURAIN G, DESCAMPS-LATSCHA B: Immune deficiency of the uremic patient. *Adv Nephrol* 19:259–275, 1990
93. ZAOUI P, GREEN W, HAKIM RM: Hemodialysis with cuprophane membrane modulates interleukin-2 receptor expression. *Kidney Int* 39:1020–1026, 1991
94. KAY NE, RAIJ L: Differential effect of hemodialysis membranes on human lymphocyte natural killer function. *Artif Organ* 11:165–167, 1987
95. RAIJ L, KAY NE: Effect of hemodialysis membranes on human lymphocyte natural killer function. *Contr Nephrol* 59:17–25 1987
96. ZAOUI P, HAKIM RM: Natural killer-cell function in hemodialysis patients: Effect of the dialysis membrane. *Kidney Int* 43:1298–1305, 1993
97. DEGIANNIS D, CZARNECKI M, DONATI D: Normal T lymphocyte function in patients with end stage renal disease hemodialyzed with high-flux polysulfone membranes. *Am J Nephrol* 10:276–282, 1990
98. DEGIANNIS D, CZARNECKI M, HORNUNG N, RASKOVA J, RASKA K JR: Mixed lymphocyte reaction-induced release of soluble IL-2 receptor. *Transplantation* 51:518–523, 1991
99. DONATI D, DEGIANNIS D, COATES N, RASKOVA J, RASKA K JR: Effects of hemodialysis on activation of lymphocytes: Analysis by an *in vitro* model. *J Am Soc Nephrol* 2:1490–1497, 1992
100. LEVIN NW, ZASUWA G, DUMLER F: Effect of membrane types on causes of death in hemodialysis patients. *J Am Soc Nephrol* (abstract) 2:335, 1991
101. HORNBERGER JC, CHERNEW M, PETERSEN J, GARBER AM: A multivariate analysis of mortality and hospital admissions with high-flux dialysis. *J Am Soc Nephrol* 3:1227–1237, 1993
102. CAPPEL R, VANBEERS D, LIESNARD C, DRATWA M: Impaired humoral and cell mediated immune response in dialyzed patients after influenza vaccination. *Nephron* 33:21–25, 1983
103. CONGER JD: Does hemodialysis delay recovery from acute renal failure? *Semin Dial* 3:146–148, 1990

104. Solez K, Morel-Moroger L, Sraer JD: The morphology of "acute tubular necrosis in man." *Medicine* 58:362–376, 1979
105. Conger JD, Robinette JB, Hammond WS: Difference in vascular reactivity in models of ischemic acute renal failure. *Kidney Int* 39:1087–1097, 1991
106. Harris KPG, Schreiner GF, Klahr S: Effect of leukocyte depletion on the function of the post-obstructed kidney in the rat. *Kidney Int* 36:210–215, 1989
107. Badr KF, Schreiner GF, Wasserman M, Ichikawa I: Preservation of the glomerular capillary ultrafiltration coefficient during rat nephrotoxic serum nephritis by a specific leukotriene D4 receptor antagonist. *J Clin Invest* 81:1702–1709, 1988
108. Linas SL, Whittenburg D, Parsons P, Repine JE: : Mild renal ischemia activates primed neutrophils to cause acute renal failure. *Kidney Int* 42:610–616, 1992
109. Schulman G, Fogo A, Gung A, Badr K, Hakim R: Complement activation retards resolution of acute ischemic renal failure in the rat. *Kidney Int* 40:1069–1074, 1991
110. Hakim RM, Wingard RL, Lawrence P, Parker RA, Schulman G: Use of biocompatible membranes improves outcome and recovery from acute renal failure. *J Am Soc Nephrol* (abstract) 3:367, 1992
111. Hakim RM, Levin N: Malnutrition in hemodialysis patients. *Am J Kidney Dis* 21:125–137, 1993
112. Guiterrez A, Alvestrand A, Wahren J, Bergstrom J: Effect of *in vivo* contact between blood and dialysis membranes on protein catabolism in humans. *Kidney Int* 38:487–494, 1990
113. Guiterrez A, Alvestrand A, Bergstrom J: Membrane selection and muscle protein catabolism. *Kidney Int* 42:S86–S90, 1992
114. Dinarello CA, Koch KM, Shaldon S: Interleukin-1 and its relevance in patients treated with hemodialysis. *Kidney Int* 33 (Suppl 24):S21–S26, 1988
115. Lindsay RM, Spanner EA, Heidenheim P, Kortas C, Blake PG: PCR, K_t/V and membrane. *Kidney Int* 43 (Suppl 41):S268–S273, 1993
116. Chanard J, Brunois JP, Melin JP, Lavaud S, Toupance O: Long term results of dialysis therapy with a highly permeable membrane. *Artif Organs* 6:262–266, 1982
117. Wolfe RA, Gaylin DS, Port FK, Held PJ, Wood CL: Using USRDS generated mortality tables to compare local ESRD morbidity rates to national rates. *Kidney Int* 42:991–996, 1992
118. Lowrie EG, Lew NL, Liu Y: Evaluation of facility attributes associated with the standardized mortality ration (SMR). Internal Memorandum, NMC. March 30, 1993
119. Vanholder R, Ringoir S: Polymorphonuclear cell function and infection in dialysis. *Kidney Int* 42:S91–S95, 1992
120. Hakim RM, Depner TA, Parker TF: Adequacy of hemodialysis. *Am J Kidney Dis* 20:107–123, 1992
121. Lysaght M, Vonesh E, Ibels L: Decline of residual renal function in hemodialysis and CAPD patients: A risk adjusted growth-function analysis. *Am Soc Artif Int Org* (in press)
122. Gung A, Schulman G, Hakim R: Hemodialysis membrane choice influences maintenance of residual renal function (RRF) in an animal model. *J Am Soc Nephrol* (abstract) 2:327, 1991
123. Deppisch R, Schmidt V, Bommer J: Fluid phase generation of the terminal complement complex C5b-9 as a novel index of biocompatibility. *Kidney Int* 37:696–706, 1990
124. Correa-Rotter R, Hostetter TH, Nath KA, Manivel C, Rosenberg ME: Interaction of complement and clustering in renal injury. *J Am Soc Nephrol* 3:1172–1179, 1992
125. Couser WG: Mediation of immune glomerular injury. *J Am Soc Nephrol* 1:13–29, 1990
126. Knudsen F, Nielsen AH, Pedersen JO, Jersild C: On the kinetics of complement activation, leucopenia and granulocyte-elastase release induced by haemodialysis. *Scand J Clin Lab Invest* 45:759–766, 1985
127. Perkowski SZ, Havill AM, Flynn JT, Gee MH: Role of intrapulmonary release of eicosanoids and superoxide anion as mediators of pulmonary dysfunction and endothelial injury in sheep with intermittent complement activation. *Circ Res* 53:574–583, 1983
128. Ward PA, Till GO, Hatherill JR, Annesley TM, Knunkel RG: Systemic complement activation, lung injury, and products of lipid peroxidation. *J Clin Invest* 76:517–527, 1985
129. Langlois PF, Gawryl MS: Accentuated formation of the terminal C5b-9 complement complex in patient plasma precedes development of the adult respiratory distress syndrome. *Am Rev Respir Dis* 138:368–375, 1988
130. Hakim RM, Lowrie EG: The relative effect of leukopenia and dialysate composition on the dialysis-associated hypoxemia. *Proc Dial Transplant Forum* 10:190–195, 1980
131. Bariety J, Hinglais N, Bhakdi S, Mandet C, Rouchon M, Kazatchkine M: Immunohistological study of complement S protein (Vitronectin) in normal and diseased human kidneys: Relationship to neoantigens of the C5b-9 terminal complex. *Clin Exp Immunol* 75:76–81, 1989
132. Zalman LS, Wood LM, Muller-Eberhard HJ: Isolation of a human erythrocyte membrane protein capable of inhibiting the expression of homologous complement transmembranous channels. *Proc Natl Acad Sci USA* 83:6975–6979, 1986