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Biocompatibility of dialysis membranes: Effects of chronic complement activation

RAYMOND M. HAKIM, DOUGLAS T. FEARON, and J. MICHAEL LAZARUS
with the technical assistance of CYNTHIA S. PERZANOWSKI

Departments of Medicine and Immunology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

Biocompatibility of dialysis membranes: Effects of chronic complement activation. The ability of three dialysis membranes (cuprophane, cellulose acetate, and polymethylmethacrylate) to activate complement was studied prospectively in ten chronic dialysis patients using new and reused membranes. Patients were dialyzed for 1 month with each type of membrane. New cuprophane membranes caused the most intense activation, while polymethylmethacrylate (PMMA) surfaces caused the least degree of complement activation. Reuse decreases the capacity of the cuprophane membrane to activate complement but does not significantly alter the capacity of cellulose acetate membranes. The extent of complement activation paralleled the ability of these membranes to induce neutropenia. Recurrent dialysis with new cuprophane and cellulose acetate membranes leads to a decrease in pre-dialysis and "rebound leukocytosis" neutrophil count, as well as a more intense activation of complement and an enhanced endogenous clearance of products of complement activation. The clinical sequelae of recurrent complement activation are discussed.

Biocompatibilité des membranes de dialyse: effets de l'activité chronique du complément. La capacité de trois membranes de dialyse (cuprophane, acétate de cellulose, et polyméthylméthacrylate) d'activer le complément a été étudiée prospectivement chez dix dialysés chroniques en employant des membranes neuves ou déjà utilisées. Les malades ont été dialysés pendant 1 mois avec chaque type de membrane. Les membranes neuves en cuprophane entrainaient l'activation la plus intense, tandis que les surfaces en polyméthylméthacrylate (PMMA) étaient responsables du moindre degré d'activation du complément. La réutilisation diminue la capacité de la membrane de cuprophane à activer le complément mais ne modifie pas significativement celle des membranes en acétate de cellulose. L'importance de l'activation complémentémique était parallèle à la capacité de ces membranes d'induire une neutropénie. Des dialyses répétées avec des membranes neuves de cuprophane ou d'acétate de cellulose conduisent à une baisse de la numération des neutrophiles prédialytique et à la "hyperleucocytose de rebound," à une activation plus intense du complément et à une stimulation de l'élimination endogène des produits de l'activation du complément. Les conséquences cliniques d'une activation répétée du complément sont discutées.

Recent studies confirm that the complement system is activated during hemodialysis [1, 2]. This activation is more intense with cuprophane membrane than cellulose acetate [3] or polyacrylonitrile (PAN) membranes [1] and for cuprophane, it attenuates with reuse [4, 5]. However, to our knowledge, the long-term effects of chronic activation of complement during dialysis has not been studied.

To investigate the differences in the ability of different membranes to activate complement, we initiated a prospective study of complement activation in ten chronic hemodialysis patients, using three different hollow fiber membranes, namely cuprophane, cellulose acetate, and polymethylmethacrylate (PMMA) membrane dialyzers. The latter membrane is used in Europe and Japan and is undergoing clinical trials in the United States. By using the same patient population on dialyzers with the same hollow fiber configuration and surface area, we were able to highlight important differences between these membranes in terms of their capacity to activate complement and cause neutropenia, both acutely and chronically.

Methods

Ten long-term chronic hemodialysis patients undergoing 4-hr maintenance hemodialysis periods three times each week were chosen for the study. Informed consent was obtained. None of the patients were known to have had recent or current symptoms of fluid overload or cardiorespiratory diseases, and none were known to be sensitive to dialysis membrane materials. Patients were dialyzed according to their schedule in a facility practicing reuse, and fluid was removed to achieve their respective dry weight. Maximum blood flow was 300 ± 50 ml/min and dialysate flow was maintained at 500 ml/min.

Each patient was dialyzed with three different hollow dialyzers, namely, the HPF-100 (Erika, New Jersey) using cuprophane fibers, the CD-4000 (Cordis-Dow, California) using cellulose acetate fibers, and the TORAY B2-150 (TORAY Industries, Tokyo, Japan) using PMMA fibers. In the first part of the study, each patient was dialyzed for 1 month, which equated to 13 dialysis sessions, on each type of dialyzer using only new, first-use dialyzers each time, and successively changed to the other types of membrane dialyzer. The sequence of dialyzer membrane material was the following: cuprophane, cellulose acetate, and finally PMMA. All dialyzers including new dialyzers were packed in a 2% solution of formaldehyde, rinsed and primed in the usual manner, and tested to be free of formaldehyde by the modified Schiff reagent (sodium meta-bisulfite), which is sensitive to less than 4 μg/ml of formaldehyde [6]. After each use, dialyzers were washed and packed with 2% formaldehyde solution according to standard

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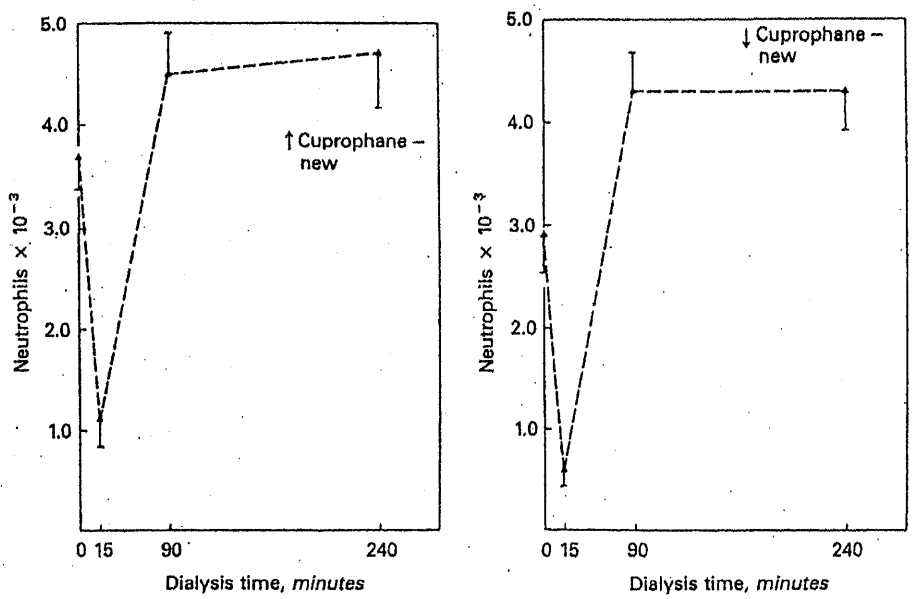

Fig. 1. *Neutrophil count during dialysis with new cuprophane membrane (↑ indicates the beginning of the new cuprophane dialyzer phase, ↓ indicates end of new cuprophane dialyzer phase).*

reuse practice. After termination of the new dialyzer phases of the study, the same patients were then dialyzed with their own reused dialyzers for another month on each type of reused membrane.

Blood samples were drawn predialysis from the arteriovenous fistula of the patient, and then at 15, 90, and 240 min after initiation of dialysis, simultaneously from the arterial (afferent) and venous (efferent) lines of the dialyzer. Blood samples were drawn in EDTA tubes, centrifuged, and separated immediately; samples were stored in duplicate polypropylene tubes at −70°C until processing. Samples were thawed only once for processing. Blood samples drawn from patients during the reuse phase were all drawn during the third use of the dialyzer. Blood samples for white blood cell (WBC) analysis were also drawn simultaneously from the afferent and efferent lines and differential WBCs were performed on 100 cells. Neutrophil counts taken from the efferent and afferent samples at all sampling times were similar for all dialyzer membranes tested. Neutrophil counts reported are those measured in afferent samples.

Measurements of complement activation. Radioimmunoassay measurements of C3adesarg, C4adesarg, and C5adesarg were carried out with commercial kits developed by the Upjohn Company, Kalamazoo, Michigan, using techniques developed by Chenoweth and Hugli [7, 8] for RIA measurements of C3adesarg and C5adesarg and by Gorski, Hugli, and Muller-Eberhard [9] for C4adesarg. Cross-reactivity of C3adesarg, C4adesarg, and C5adesarg was estimated at less than 1% [8].

Total C3 was measured in pre-dialysis samples at the beginning and end of each phase using radial immunodiffusion assay, by the endpoint technique (Kallestad Laboratories, Austin, Texas).

All values are reported as mean ± SEM. Statistical analysis was done by the pair-wise two-tailed Student's *t* test.

Results

Initiation of dialysis using new cuprophane membranes results in a rapid decline of neutrophils from the pre-dialysis value of 3.7 ± 0.32 × 10^3 cells/mm^3, such that by 15 min, the neutrophil count in the circulation is 1.1 ± 0.16 × 10^3 cells/mm^3 or 30% of its pre-dialysis value (neutropenic phase); thereafter, the neutrophil count increases, and 60 min after initiation of dialysis the neutrophil count returns to approximately baseline level, and increases further to 4.7 ± 0.41 × 10^3 cells/mm^3 (127% its pre-dialysis value) at 4 hr (rebound leukocytosis phase) (Fig. 1 and Table 1). Comparison of the cyclical variation of neutrophils at the beginning and the end of the month on new cuprophane dialyzers (Fig. 1) shows that the pre-dialysis neutrophil count was significantly decreased from a level of 3.7 ± 0.32 × 10^3 cells/mm^3 to a level of 2.9 ± 0.37 × 10^3 cells/mm^3 ($P \leq 0.01$); furthermore, the extent of neutropenic response appears to be greater with the nadir in neutrophil count as low as 0.6 ± 0.16 × 10^3 cells/mm^3, or 20% its pre-dialysis value; the number of neutrophils in the neutrophilic phase is also lower ($P \leq 0.07$, Table 1).

Dialysis using new cellulose acetate membranes and new PMMA membrane dialyzers results in similar changes although attenuated in magnitude, particularly for the PMMA membrane. For example, the nadir in neutrophil count with the cellulose acetate membrane reaches 78% its pre-dialysis value

Table 1. Neutrophil counts during dialysis with new membranes (mean ± SEM) × 10^{-3}/mm^3

Time	Cuprophane	Cellulose acetate	PMMA
Beginning of phase			
Pre	3.7 ± 0.32	3.8 ± 0.39	3.5 ± 0.43
15	1.1 ± 0.16	3.0 ± 0.32	3.0 ± 0.34
90	4.5 ± 0.31	4.8 ± 0.36	3.8 ± 0.47
240	4.7 ± 0.41	4.6 ± 0.41	3.6 ± 0.31
End of phase			
Pre	2.9 ± 0.37[a]	3.2 ± 0.36[c]	3.4 ± 0.37
15	0.6 ± 0.16[b]	2.5 ± 0.27[b]	3.1 ± 0.33
90	4.3 ± 0.37	4.3 ± 0.54	3.8 ± 0.34
240	4.3 ± 0.39[c]	4.3 ± 0.52	4.1 ± 0.35

[a] $P \leq 0.01$, from the corresponding value at the beginning of phase.
[b] $P \leq 0.05$, from the corresponding value at the beginning of phase.
[c] $P \leq 0.07$, from the corresponding value at the beginning of phase.

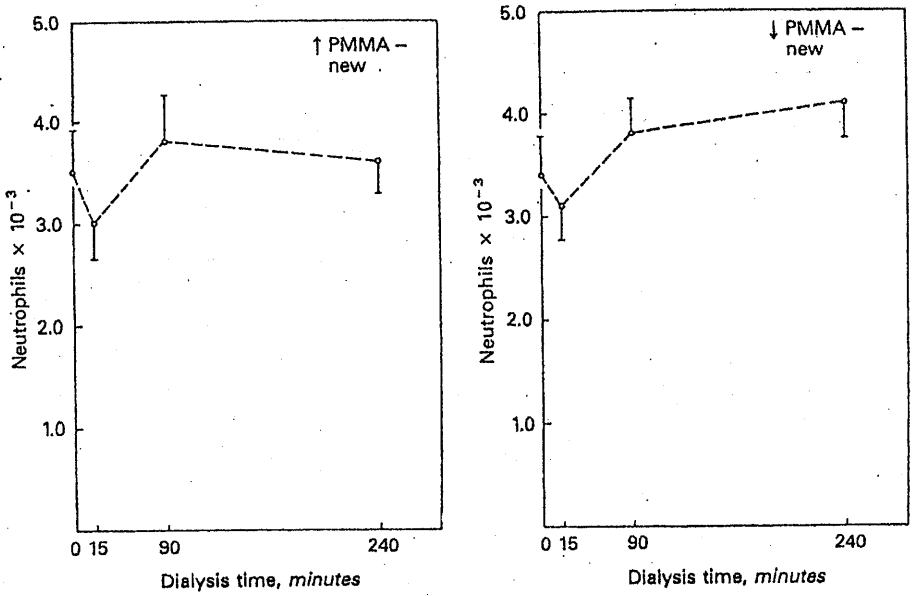

Fig. 2. *Neutrophil count during dialysis with PMMA membrane dialyzers.* No significant change was seen in these counts at the end of the month.

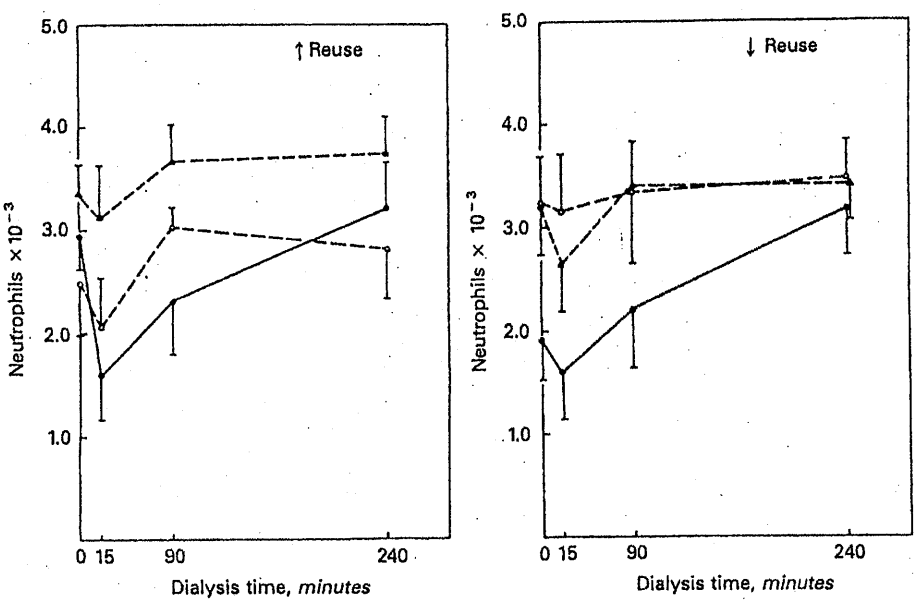

Fig. 3. *Effect of reuse on neutrophil counts.* All dialyzers were tested during the third use. Symbols are: ↑, indicates values obtained at the beginning of the reuse phase; ↓, indicates values obtained at the end of the reuse phase; ▲--▲, cuprophane; O--O, PMMA; ●—●, cellulose acetate.

Table 2. Neutrophil counts during dialysis with reused membranes (mean ± SEM) × 10^{-3}/mm^3

Time	Cuprophane	Cellulose acetate	PMMA
Beginning of phase			
Pre	3.3 ± 0.32	2.9 ± 0.31	2.5 ± 0.49
15	3.1 ± 0.53	1.6 ± 0.43	2.1 ± 0.47
90	3.6 ± 0.36	2.3 ± 0.52	3.03 ± 0.22
240	3.7 ± 0.35	3.2 ± 0.44	2.8 ± 0.47
End of phase			
Pre	3.2 ± 0.47	1.9 ± 0.37[a]	3.3 ± 0.44[a]
15	2.7 ± 0.43	1.6 ± 0.45	3.16 ± 0.55
90	3.4 ± 0.45	2.2 ± 0.56	3.33 ± 0.69
240	3.4 ± 0.33	3.1 ± 0.45	3.47 ± 0.38

[a] $P < 0.05$, from the corresponding value at the beginning of the phase.

(Table 1), whereas the nadir in neutrophil count is only 85% its pre-dialysis value for the PMMA membrane (Fig. 2), all occurring at 15 min after the initiation of dialysis. After 1 month of dialysis on the new cellulose acetate membranes, changes similar to those seen with cuprophane membranes were observed. Thus, there was a decrease in the pre-dialysis, nadir, and rebound neutrophil count, as seen in Table 1. On the other hand, for the PMMA membrane, neither the pre-dialysis value nor the nadir in neutrophil count was significantly different from the beginning to the end of the month (Fig. 2 and Table 1); instead there was an increase in the maximum neutrophil count at 240 min.

During the reuse phase, the extent of neutropenia seen early during dialysis was markedly attenuated for the cuprophane membrane. Thus, during the third reuse of the cuprophane

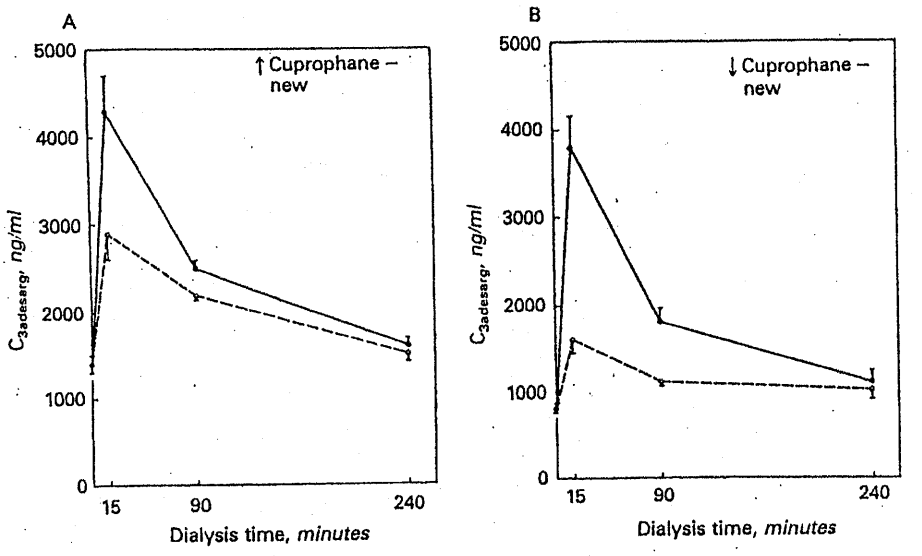

Fig. 4. *C3adesarg level for cuprophane membrane dialyzers as a function of dialysis time.* Symbols are: (↑, indicates beginning of new cuprophane dialyzer phase; ↓, indicates C3adesarg level after 1 month of new cuprophane membrane dialysis; ●—●, efferent sample; ○—○, afferent sample.

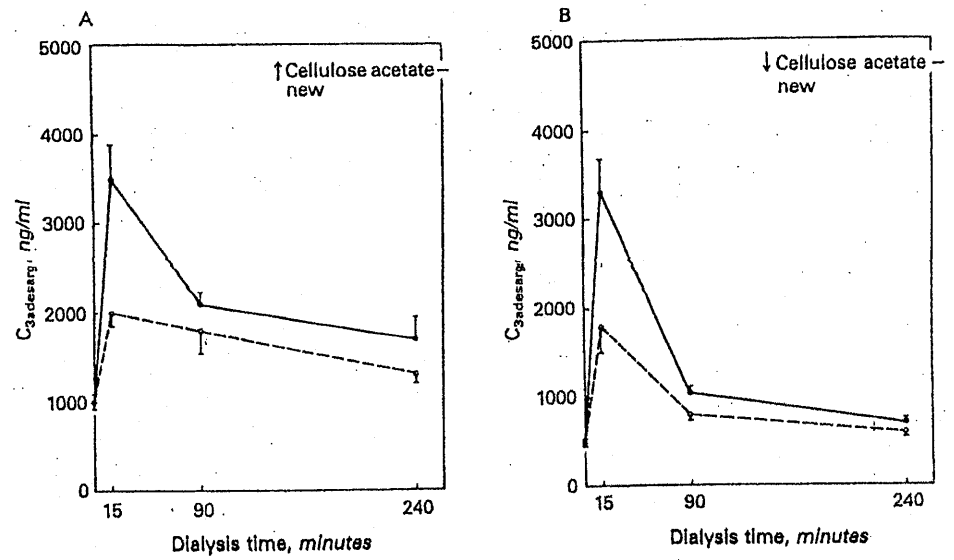

Fig. 5. *C3adesarg level for cellulose acetate membrane dialyzers as a function of dialysis time.* Symbols are: (↑ and ↓ indicate the beginning and end of 1 month of new cellulose acetate dialyzers, respectively; ●—●, efferent sample; ○--○, afferent sample.

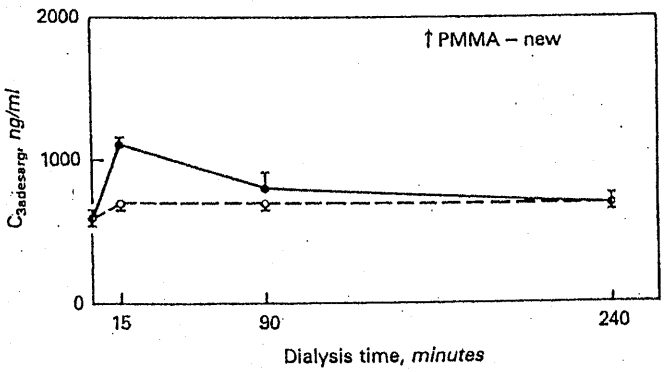

Fig. 6. *C3adesarg level for PMMA membrane dialyzers as a function of dialysis time.* Levels at the end and the beginning of 1 month were identical. Symbols are: ●—●, efferent sample; ○--○, afferent sample.

membrane dialyzer, the minimum neutrophil count seen at 15 min was 93% its pre-dialysis value (Fig. 3); similarly, the neutrophilic phase was also attenuated. However, the extent of neutropenia for the cellulose acetate membrane was less affected with reuse; thus, during the third use at 15 min, it was still 54% of the predialysis value. For the PMMA membrane, the extent of neutropenia and rebound leukocytosis was not markedly different during the reuse phase and was similar to the limited cyclical variation observed during the new dialyzer phase of PMMA. Pre-dialysis neutrophil counts at the end of 1 month of reuse with each type of dialyzer, seen in Figure 3B and Table 2, were not significantly different for the cuprophane membrane, but were significantly lower for the cellulose acetate dialyzers and significantly higher for PMMA membrane dialyzers ($P \leq 0.05$).

The C3adesarg level in simultaneously drawn efferent and afferent samples of cuprophane dialyzers at the beginning of the new dialyzer phase is shown in Figure 4. It is seen that at the beginning of the phase on new cuprophane dialyzers, the C3adesarg level rapidly rose after the initiation of dialysis, such that by 15 min, the concentration in the efferent sample was 4343 ± 417 ng/ml (309% its pre-dialysis level). Thereafter, it decreased, and was 176% and 115% its pre-dialysis level at 90 and 240 min respectively after initiation of dialysis. However,

Table 3. Pre-dialysis C3 level by radioimmunodiffusion assay (mean ± SEM), *mg/ml*

Type of dialysis membrane	Beginning of month	End of month
Cuprophane	124.3 ± 14.1	103.5 ± 11.0
Cellulose acetate	125.7 ± 9.5	121.5 ± 14.2
PMMA	96.5 ± 21	107 ± 20

even at 240 min, the efferent concentration of C3adesarg was significantly greater than its pre-dialysis value ($P = 0.008$). Arterial (afferent) samples showed similar patterns, but lesser in magnitude, and at 240 min the C3adesarg level was not significantly different from pre-dialysis value. Of interest is that the difference in the simultaneously drawn C3adesarg level in the arterial and venous samples is greatly in excess of what can be accounted for by hemoconcentration at 15 and 90 min ($P \leq 0.03$), indicating a continuous activation of complement up to 90 min. However, at times beyond 15 min, the difference between the arterial and venous samples narrows, reflecting a slower rate of activation and simultaneous endogenous clearance of these biologically active products, and at 240 min, the difference between the afferent and efferent samples was not statistically significant.

The comparison of efferent and afferent samples for cuprophane at the beginning and the end of the month indicate a widening difference between the efferent and afferent concentration at the end of the month, both at 15 and 90 min ($P \leq 0.01$). In addition, both the pre-dialysis and the afferent levels at 240 min was significantly lower at the end of the month than at the beginning ($P \leq 0.05$), suggesting a faster endogenous clearance of C3adesarg after repetitive activation of complement during dialysis with new cuprophane membranes. For cellulose acetate membranes (Fig. 5), the rate of decline of C3adesarg level between 15 and 90 min was also higher at the end of 1 month on new cellulose acetate membranes, and the differences between the efferent and afferent samples at 15 and 90 min were also statistically significant at the end of the month ($P \leq 0.01$), whereas they were not significantly different at 90 min at the beginning of the month. At 240 min, the level of the arterial (afferent) C3adesarg level was still significantly greater than pre-dialysis values at the beginning of the month ($P \leq 0.001$), but was not significantly greater than the pre-dialysis level at the end of the month ($P = 0.1$).

PMMA membranes induce transient and minimal activation of complement, as shown by the lower rise in the efferent C3adesarg concentration at 15 min (190% its pre-dialysis value) and by the lack of significant differences between efferent and afferent samples at times beyond 15 min, both at the beginning and the end of the month (Fig. 6).

C4adesarg levels, measured on efferent and afferent samples on each of the three new dialysis membranes, were not statistically significant from pre-dialysis levels.

The only significantly elevated level of C5adesarg was found in the efferent venous sample at 15 min and was highest for cuprophane membranes, 33.5 ± 5.1 ng/ml, and was 17.7 ± 2.2 ng/ml for cellulose acetate membranes. C5adesarg was undetectable for the PMMA membrane at all times. There was a small increase, but not statistically significant, in the C5adesarg levels at the end of the month for the 15-min efferent samples.

The pre-dialysis C3 level at the beginning and end of each month on new dialysis membranes is shown in Table 3. It is seen that during the month on cuprophane, the pre-dialysis C3 level decreases, from 124.3 ± 14.1 mg/ml to 103.5 ± 11.0 mg/ml, remains stable during the cellulose acetate phase, and increases during the PMMA phase. However, none of these changes were statistically significant ($P \geq 0.1$).

Complement activation as measured by C3adesarg level was considerably attenuated during reuse. The extent of activation inversely correlated with the behavior of the neutrophil count. Thus, the highest activation with reused membranes occurred with cellulose acetate membranes and was 215% its pre-dialysis value at 15 min (Fig. 7). Complement activation remained high for cellulose acetate membranes throughout the month on reuse and was 239% its pre-dialysis value at 15 min at the end of the reuse phase. On the other hand, cuprophane membranes showed a more marked attenuation, with the maximum C3adesarg level at 15 min only 133 and 149% its pre-dialysis value at the beginning and the end of the cuprophane reuse phase, respectively. PMMA membranes did not show any significant change in their complement activating capacity with reuse, which remained low. Thus, the maximum C3adesarg level at 15 min was still 152% its predialysis value at the beginning of the reuse phase and 133% its pre-dialysis level at the end of the reuse phase ($P > 0.3$).

C4adesarg and C5adesarg levels were not significantly different from the baseline for all reused membranes and at all times measured.

Discussion

Complement activation represents one aspect of blood-materials interactions and may be considered an index of biocompatibility, because products of complement activation have several biological actions, such as leukoaggregation, histamine release from mast cells, and an increase in capillary pulmonary permeability which may contribute to adverse clinical and biochemical changes [10, 11]. Indirect evidence also suggests that chronic dialysis with complement activating surfaces may be associated with increased morbidity and mortality of dialysis patients [12–15].

The results of this study confirm that complement activation by new cuprophane and cellulose acetate membrane dialyzers persists well into dialysis, as evidenced by the significant arteriovenous differences in the C3adesarg level up to 90 min after the initiation of dialysis [1, 3]. For PMMA membranes, complement activation is least of the three membranes studied and appears to attenuate early during dialysis, such that the difference between the efferent and afferent samples is not statistically significant except at 15 min [16].

Comparison of the C3adesarg level at the beginning and the end of the month on new cuprophane or cellulose acetate membranes shows two distinct features. For both membranes, the extent of activation is more pronounced at the end of the month. For example, the peak C3adesarg level at 15 min for cuprophane membranes is 309% its pre-dialysis value at the beginning of the month, and 471% its pre-dialysis value at the end of the month. Similarly, for cellulose acetate membranes, the

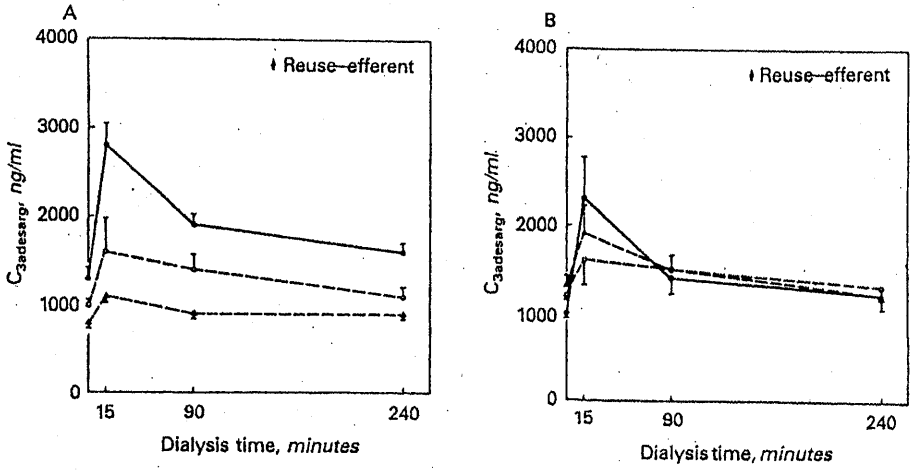

Fig. 7. *C3adesarg level for reused dialyzers.* All sampling done during the third reuse of each dialyzer. Symbols are: ↑ and ↓ indicate beginning of the month and end of the month values, respectively; ●—●, cellulose acetate; ▲--▲, cuprophane; O--O, PMMA.

peak C3adesarg level is 342% and 615% pre-dialysis level at the beginning and the end of the month, respectively.

Despite the greater extent of activation at the end of the month, the rate of clearance of C3adesarg (as assessed by differences in efferent and afferent samples and the lower pre-dialysis value) is also greater at the end of the month for both cuprophane and cellulose acetate membranes, suggesting enhanced endogenous clearances of these products. For example, the ratio of the afferent to efferent sample at 90 min at a time when complement activation is minimal, decreases from 0.87 to 0.66 for cuprophane membrane and from 0.88 to 0.76 for cellulose acetate membranes ($P \leq 0.03$), whereas it remains approximately 1.0 for the PMMA membrane. Thus, recurrent dialysis with complement activating surfaces appears to lead to a greater activation as well as enhanced clearance of complement products, suggesting that assessment of complement activation during hemodialysis must be considered with prior dialytic history.

The explanation of this phenomenon is not clear at present. Both C3 and factor B are substrates for complement activation via the alternative pathway and increased levels after 1 month of repetitive activation of the complement system may explain the greater extent of activation at the end of the month. However, C3 declines with repetitive complement activation, and increases during the PMMA membrane phase. Depletion of the inhibitory factors of this pathway such as Factors H or I (C3b inactivator) may provide an explanation, but there is at present no experimental evidence for such a postulate [17, 18].

The failure to detect a significant increase in C4adesarg level during hemodialysis constitutes strong evidence that the classical pathway is not activated, because activation of this pathway leads to the generation of approximately equimolar amounts of C3adesarg and C4adesarg, while the affinity of mast cell receptors for C4adesarg is several orders of magnitude lower than that for C3adesarg [9, 10, 19]. Despite the evidence for vigorous complement activation during dialysis, C5adesarg was detected only at 15 min after initiation of dialysis with cuprophane or cellulose acetate membranes. The rapid and irreversible binding of C5adesarg to specific receptors on neutrophils and monocytes [20], and its short half-life of less than 2 min in the circulation [21], would preclude its detection at times other than the maximum complement activation and associated maximum neutropenia. The differences between this study and that of Chenoweth et al [1], reporting elevation of C5adesarg at 240 min, is difficult to explain at present.

Confirming previous studies [4, 5], reuse of these membranes significantly attenuates the degree of neutropenia and complement activation; however, the results of this study indicate that the extent of attenuation depends on the type of membrane considered. Thus, whereas the reuse of the cuprophane membrane significantly decreases its ability to activate complement and induce neutropenia, for cellulose acetate membrane reuse affects its biocompatibility to a lesser degree and this membrane, even in the reuse phase, leads to recurrent activation of complement and induces cyclical variation in neutrophil count and a decrease in predialysis neutrophil count. The PMMA membrane's capacity to activate complement remains low and unchanged with reuse.

The mechanism for the decrease in complement activation during dialysis and the improved biocompatibility of cuprophane with reuse is likely to be due to specific deposition of complement fragments such as C3b on the activating surface and its subsequent inactivation [4, 22, 23], as well as non-specific deposition of fibrin on dialyzer membrane surfaces [24]. Differences in biocompatibility between reused cellulose acetate and cuprophane may also be due to differences in the stability of the covalent binding of C3b to these surfaces during the reuse procedure [3, 25].

The decrease in the pre-dialysis neutrophil count in conjunction with a decrease in the rebound leukocytosis after recurrent complement activation with new cuprophane and cellulose acetate membranes as shown in this study may reflect a decrease in the ability of the bone marrow to respond [26–29] and/or a decrease in the half-life of neutrophils after degranulation [30], which may be a factor in the clinical observation of increased morbidity [12] and mortality [13] in patients using new membrane dialyzers only, since infection accounts for a substantial percentage of morbidity of dialysis patients [31]. A decrease in the phagocytic abilities of the pre-dialysis neutrophil after recurrent complement activation (unpublished observation) may also play a synergistic role. Differences in the ability of complement activating surfaces to induce a more pronounced hypoxemia than noncomplement activating surfaces [16, 32] may also explain the increase in intradialytic symptoms such as chest pain and back pain seen with new cuprophane membranes [3, 14]; similarly, differences in mor-

bidity of patients dialyzed with non-complement activating membranes such as PAN and those dialyzed with cuprophane may also be due to their respective differences in their ability to activate complement [15].

In summary, different dialysis membranes show significant differences in their ability to activate complement, an index of biocompatibility [33]. Recurrent dialysis with complement activating surfaces leads to a more pronounced pre-dialysis neutropenia, a decrease in rebound leukocytosis and greater activation, as well as enhanced clearance of complement products. Dialysis with reused membranes significantly attenuates their ability to activate complement, albeit to different degrees, depending on the type of membrane. PMMA membrane dialyzers appear to be the most biocompatible hollow fiber membranes tested.

Acknowledgments

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Reprint requests to Dr. R. M. Hakim, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA

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