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Hemodialysis-Associated Neutropenia and Hypoxemia: The Effect of Dialyzer Membrane Materials

Raymond M. Hakim, Edmund G. Lowrie[1]

Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and The Kidney Center, Boston, Mass., USA

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Abstract. The fall in white blood cells (WBC) and arterial oxygen pressure that occurs during hemodialysis was investigated as a function of different dialysis membranes and different sterilization methods. 8 chronic hemodialysis patients were studied and each was dialyzed with three different membranes: cellulosic hollow fiber, polyacrylonitrile flat sheet and polymethylmethacrylate hollow fiber. Each dialyzer was studied with a dry sterilization method and after formalin treatment. Arterialized blood gas, bicarbonate and WBC were drawn at various intervals throughout dialysis. The effect of the sterilization method was minimal. Cellulosic membranes were shown to cause significantly more neutropenia ($p < 0.001$) and hypoxemia ($p < 0.01$) than the other two membranes. No significant differences was seen in pH, PCO_2 and bicarbonate. The results indicate differences in biocompatibility between different membranes. Clinical implications are discussed.

Introduction

A profound but reversible leukopenia has been well documented during the first hour of dialysis therapy [1–4] and has become an accepted side-effect of artificial-kidney treatment. Similarly, a fall in arterial oxygen tension (PO_2) has also been noted to occur during the hemodialysis procedure [5–8]. While the mechanisms of these two phenomena and their interrelationships have been the subject of considerable debate [4–9], the effect, if any, of different dialysis membranes on the hypoxemia and neutropenia has not been evaluated extensively [10–12].

Until recently, the only commercially available dialysis membranes were manufactured from a cellulosic material, either dissolved in sodium hydroxide and then regenerated in an acid bath (cellophane) or dissolved in an ammonia solution of cupric oxide before regeneration in an acid bath (cuprophane). Recently, polyacrylonitrile (PAN) membranes have been introduced commercially in the USA [13] and are being used with increasing frequency because of their higher clearance for middle molecules and higher ultrafiltration capacity [14]. Similarly, polymethylmethacrylate (PMMA) hollow fiber artificial kidneys, which also exhibit excellent small- and middle-molecule clearance and have a high ultrafiltration capacity, have become available for clinical use in Europe and Japan and are undergoing trials in the USA [15].

The present study was undertaken to examine the effect of the cellulosic and noncellulosic membranes on the dialysis-associated hypoxemia and neutropenia – as examples of known biotoxicity – in an effort to clarify the mechanisms of these two phenomena and their possible interrelationship. Since the sterilization methods of dialyzers used in previous studies have not been specified and because there exists the possibility of a specific interaction between sterilization methods (specifically dilute formalin solution) and the dialysis membrane, the effect of the sterilization method on each membrane was also studied.

Materials and Methods

Eight long-term chronic-hemodialysis patients undergoing thrice weekly, 5 h each, maintenance hemodialysis were chosen for the study. Relevant characteristics of these patients are shown in table I. In-

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Table I. Characteristics of patients participating in the study

Patient	Age	Sex	Diagnosis	Access	Smoker	Years on dialysis
P.S.	33	F	glomerulonephritis	fistula	no	8
J.N.	66	M	gouty nephropathy	fistula	no	3
I.V.	64	F	Goodpasture's	fistula	no	3
R.L.	57	F	hypertension	shunt	occasional	0.5
R.W.	34	M	diabetic nephropathy	fistula	former	3
J.L.	50	M	hypertension	fistula	yes	3
R.H.	37	M	glomerulonephritis	fistula	yes	4
O.P.	56	F	pyelonephritis	fistula	no	3

All patients had residual renal function less than 1.0 ml/min.

formed consent was obtained prior to the study. None of the patients were known to have had recent or current symptoms of fluid overload or cardiorespiratory diseases. Patients were dialyzed according to their regular schedule, and fluid was removed to achieve their 'dry weight' – 2.5 ± 1.0 kg on the average. Blood flow varied somewhat between patients and was in the range of 250–300 ml/min.

Each patient was dialyzed with three different first-use dialyzers; namely, the Cordis-Dow (C-D) 1.3 m^2 using cellophane hollow fibers, the Hospal RP-6 using a PAN flat sheet membrane, and the Toray Industries' B-2-M, manufactured with PMMA hollow fibers. Each patient was dialyzed twice with each type of dialyzer – in one instance, the dialyzer was 'dry'-sterilized (gamma rays for Toray and ethylene oxide for C-D and RP-6) and in the other that it was sterilized with formalin (wet sterilization). Formalin-sterilized dialyzers were washed and primed in the usual manner, and were tested to be free of formalin by the modified Schiff reagent, which is sensitive to 30 ppm of formalin. The dialysate used was Erilyte 8107 which, when diluted appropriately, contains acetate in a concentration of 40 mEq/l and sodium in a concentration of 138 mEq/l. A single-pass counterflow system of dialysate circulation was used in all cases. Dialysate flow was at a rate of 500 cm^3/min.

Arterialized blood samples were drawn anaerobically from the arterial line prior to the start of dialysis and at intervals of 7.5, 15, 30, 60, 120, and 180 min after the start of dialysis. Samples for pH, PO_2 and PCO_2 were drawn in a heparinized syringe. Blood samples from the dialyzer arterial line were previously shown to represent true arterial blood values [16, 17]. All samples were kept on ice until just prior to measurement, which was less than 0.5 h from the time of sampling [18]. Blood samples for total CO_2 measurement were drawn in a glass tube and centrifuged. Aliquots of supernatant plasma were used to measure total plasma CO_2. Bloods for the white blood cell (WBC) and differential counts were collected in EDTA tubes.

Blood gases were measured using the Corning Medical (Medfield, MA) Automatic pH/Blood Gas System, Model 161. The PCO_2 electrode was of the Stow-Severinghaus type and the PO_2 electrode was of the Clark type. Calibration with two known gaseous standards was performed before each measurement. In addition, calibration with tonometered liquids for PO_2, PCO_2, pH and total CO_2 (General Diagnostics, N.H.) was done at the beginning of each set of experiments. Accuracy of PO_2 measurement at PO_2 of 100 mm Hg was 2.1% and repeatability was ±1.0 mm Hg. Accuracy of PCO_2 measurement at a PCO_2 of 40 mm Hg was 0.8% and repeatability was ±1.0 mm Hg.

Total CO_2 was measured separately, using a Corning Medical CO_2 Analyzer, Model 960, which measures the thermal conductivity of the CO_2 evolved by reacting the plasma with lactic acid. Accuracy of total CO_2 measurement at a total CO_2 concentration of 20 mmol/l was 2.3% snd repeatability was ±1.0 mmol/l.

WBC counts were done with a Coulter Counter Model S (Miami, Fl.). Differential counts were done on 100 WBC.

Data from all patients were grouped and analyzed by the type of dialyzer (i.e. membrane) and method of prior sterilization. Analysis of variance was used to test statistical significance [19, 20]. The analytical model assumes a two-factor design (dialysis membrane and method of sterilization) and was 'blocked' by patient. Duncan's multiple-range test was also used in the evaluation of the data in table II.

Table II. Changes in the partial pressure of oxygen and WBC with different dialyzer membranes (mean ± SEM)

	Cellophane	PAN	PMMA
Minimum PO_2, % of predialysis value	79.4 ± 2.4	86.8 ± 2.5	86.2 ± 1.5
Maximum fractional, % fall in PO_2	26.9 ± 1.7	19.5 ± 1.8	19.5 ± 1.6
Minimum WBC, % of original value	34.1 ± 3.1	86.3 ± 1.9	83.4 ± 2.1
Minimum PMN, % of original value	19.5 ± 3.3	82.8 ± 2.8	74.4 ± 4.0
Minimum lymphocytes, % of original value	59.8 ± 8.7	93.0 ± 4.5	99.3 ± 8.5

Values not underlined by the same line are significantly different ($p < 0.05$) from each other by Duncan's multiple-range test.

Table III. Average initial values of all patients

	Initial values mean ± SEM
pH	7.43 ± 0.01
PO_2, mm Hg	93.6 ± 2.80
PCO_2, mm Hg	35.2 ± 0.98
TCO_2, mmol/l	22.8 ± 0.63
HCO_3, mmol/l	21.8 ± 0.57
WBC × 10^{-3} cells/mm^3	6.2 ± 0.63
pK (serum)	6.11 ± 0.01

HCO_3 is calculated from $TCO_2 - 0.03\ PCO_2$. pK is calculated from pH − 10 g [$HCO_3/0.03 \times PCO_2$] but TCO_2 and PCO_2 are measured separately.

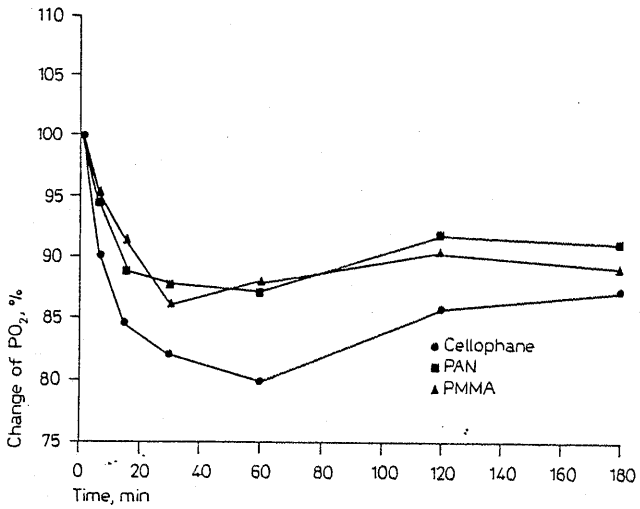

Fig. 1. Relative change of PO_2 as a function of dialysis time for different membrane materials. Values of PO_2 at 15, 30 and 60 min are significantly different ($p < 0.05$) between cellulosic and noncellulosic membranes.

Results

All parameters were converted to a percent predialysis value (100 × P/P initial) in order to reduce the effects of different predialysis values for different patients and for the same patients on different days. The average initial value for all parameters is shown in table III. All parameters are expressed as mean ± SEM.

Effect of Sterilization

There were no statistically significant differences between formalin-sterilized and dry-sterilized membranes in any parameter tested for the PMMA and cellulosic dialyzers. There was a trend toward greater hypoxemia with the formalin-pretreated PAN membrane (it must be mentioned that the Hospal RP-6 is more commonly sterilized with hypochlorite solution) and with the dry-sterilized cellulosic membrane but this was not statistically significant except at the 60-min PO_2 for the PAN membrane ($p = 0.03$). Other parameters such as pH, HCO_3 and WBC were not significantly different between the dry- and wet-sterilized membranes.

Subsequent results will thus be analyzed with the data for each dialyzer representing aggregate data for the wet- and dry- sterilized membranes.

Change in Partial Pressure of Oxygen (PO_2)

The change in PO_2 with dialysis time for the three types of dialyzers is shown in figure 1. It is seen that there is a gradual decrease in PO_2 with the initiation of dialysis, with a broad minimum, which occurs at different times for different dialyzers, followed by a gradual increase in PO_2. While there was no statistically significant difference in the percent PO_2 drop between the PMMA and PAN membranes (noncellulosic) at any time during dialysis, there was a significant difference in the percent PO_2 drop between the cellulosic and both the noncellulosic membranes at 15 min ($p \leqslant 0.05$), 30 min ($p \leqslant 0.05$) and at 60 min ($p \leqslant 0.02$).

Several points require emphasis. At any time during dialysis, the greatest change in PO_2 occurs with the cellulosic membranes. The average PO_2 of patients dialyzed with this membrane decreased to 79.4 ± 2.4% (mean ± SEM) of the initial value at 60 min. In contrast, the minimum PO_2 obtained with the non-cellulosic membranes was 86.2 ± 10.5% for the PMMA membrane and 86.8 ± 2.5% of the initial value for the PAN membrane. The time at which the maximum hypoxemia occurred was 60 min for both the cellulosic and PAN membrane while it occurred at 30 min for the PMMA membrane.

The maximum fractional PO_2 fall, defined as

$$100 \times \frac{(PO_2)\ \text{initial} - (PO_2)\ \text{minimum}}{(PO_2)\ \text{initial}}$$

which is a measure of the maximum fall in PO_2 regardless of the time at which it occurred was also significantly different between cellulosic (26.9 ± 1.6%) and noncellulosic dialyzers: 19.5 ± 2.1% for the PAN and 19.5 ± 1.6% for the PMMA membrane ($p \leqslant 0.01$).

It should also be noted that by 180 min, the PO_2 for the three types of dialyzers was still below the predialysis values and, although the hypoxemia was still more pronounced for the cellulosic membrane, there was no sta-

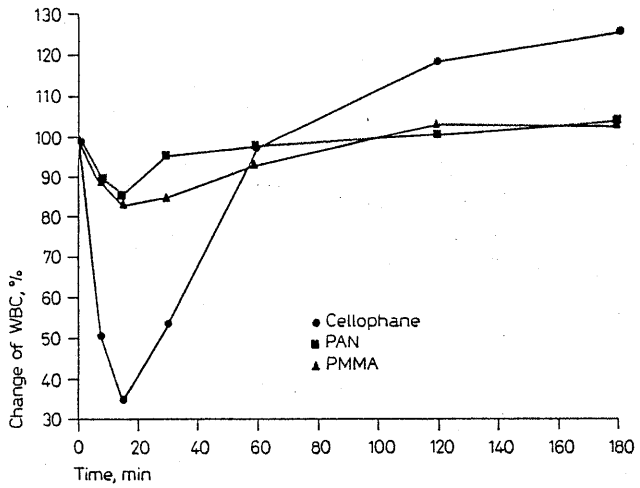

Fig. 2. Relative change of white blood cells as a function of dialysis time for different membrane materials. All values, except at 60 min, are significantly different ($p < 0.001$) between cellulosic and noncellulosic membranes.

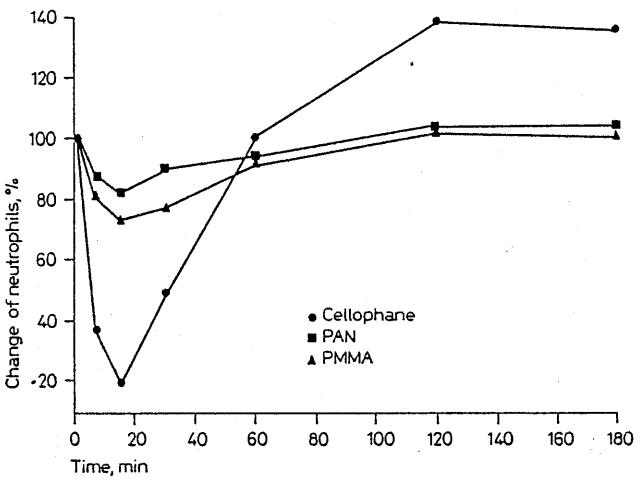

Fig. 3. Relative change of neutrophils as a function of dialysis time for different membrane materials. All values, except at 60 min, are significantly different ($p < 0.001$) between cellulosic and noncellulosic membranes.

tistical difference in PO_2 among the three types of dialyzers at that time.

WBC Counts

The relative change in WBC counts is shown in figure 2. It is evident that the fall in WBC depends strongly on the type of membrane and is more pronounced with the cellulosic membrane than with either of the noncellulosic membranes. The average WBC of patients dialyzed with

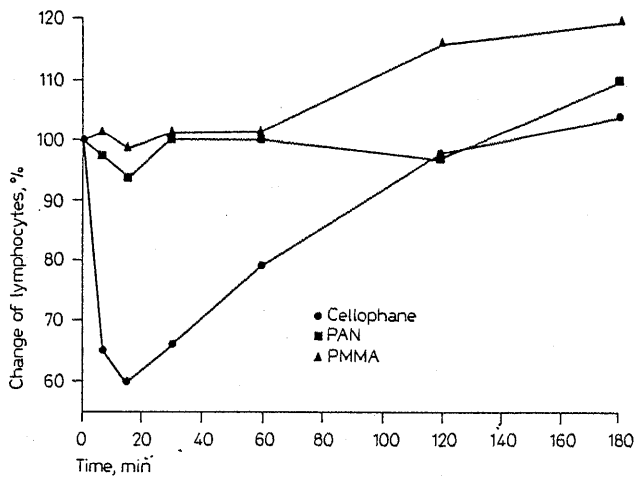

Fig. 4. Relative change of lymphocytes as a function of dialysis time for different membrane materials. Values at 7.5, 15, and 30 min are statistically different ($p < 0.001$) between cellulosic and noncellulosic membranes.

the cellulosic membrane decreased to $34.1 \pm 3.1\%$ of the predialysis value at 15 min, while it fell to only $86.3 \pm 1.9\%$ and $83.4 \pm 2.1\%$ of the initial value with the PAN and PMMA membranes, respectively.

It is perhaps more instructive to consider the changes in the neutrophils and lymphocytes separately since their interaction with the different membranes may be quite different.

The relative change in the fraction of neutrophils during dialysis, calculated from the total WBC and differential count, is shown in figure 3. The cellulosic membrane induces a significant neutropenia, with the neutrophil count decreasing to $19.5 \pm 3.3\%$ of the predialysis value at 15 min. The neutrophil count increased thereafter and following the first hour of dialysis exceeded predialysis values such that by 180 min it was $137.0 \pm 9.9\%$ of the predialysis value.

In sharp contrast to this, the percent change in the neutrophil count was considerably less with both noncellulosic membranes. The minimum level to which neutrophils fell was $82.8 \pm 2.8\%$ of the predialysis value with PAN membrane, and was $74.4 \pm 4.0\%$ with the PMMA membrane. There was no 'overshoot' observed with either of these two noncellulosic dialyzers.

While there was no statistically significant difference in the percentage change of neutrophils between the PAN and PMMA dialyzers, there was a significant difference between the cellulosic and both noncellulosic membrane dialyzers at 7.5, 15 and 30 min ($p \leqslant 0.0001$), and later at 120 ($p \leqslant 0.004$) and 180 min ($p \leqslant 0.003$).

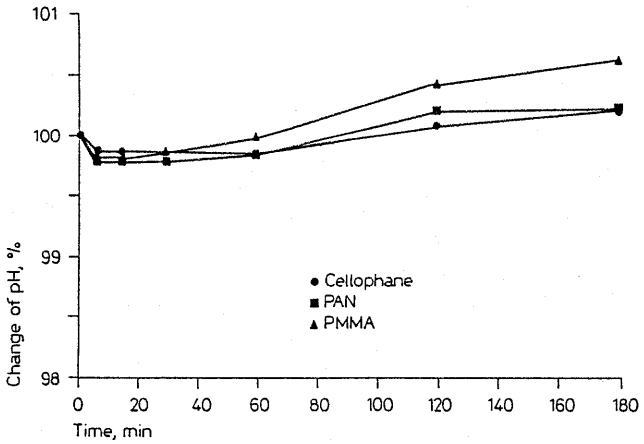

Fig. 5. Relative change of pH as a function of dialysis time for different membrane materials. The pH of the PMMA membrane at 180 min is the only significantly different value ($p < 0.02$).

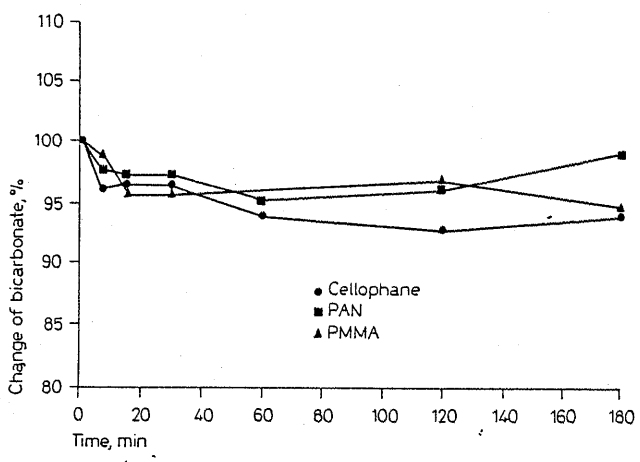

Fig. 7. Relative change of bicarbonate as a function of dialysis time for different membrane materials. No significant difference is seen between different dialyzer membranes.

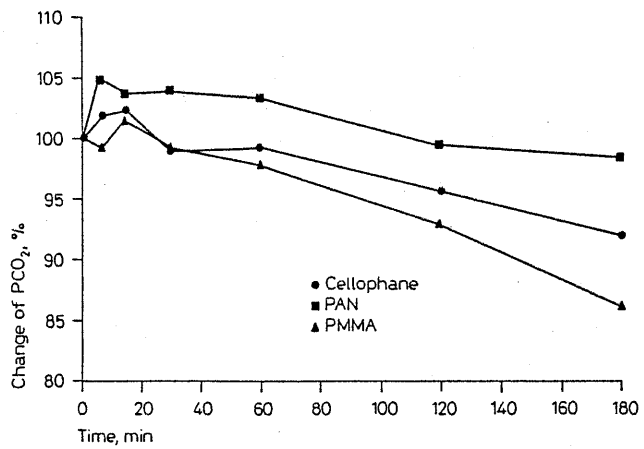

Fig. 6. Relative change of PCO_2 as a function of dialysis time for different membrane materials. The PCO_2 of the PMMA membrane at 180 min is the only significantly different value ($p < 0.03$).

Although the proportion of lymphocytes to neutrophils increased during the dialysis-induced neutropenia, the absolute number of lymphocytes fell, as shown in figure 4. The same patterns were observed as for neutrophils – albeit to a lesser extent. Thus, the greatest fall in lymphocytes occurred with the cellulosic membrane at 15 min, when the lymphocyte count fell to $59.8 \pm 8.7\%$ of the predialysis value. The minimum level observed with PAN membranes was $93.0 \pm 4.8\%$ of the predialysis value, while when patients were dialyzed with PMMA membranes lymphocytes did not decrease. There was no statistically significant difference in the pattern or severity of lymphopenia between the two noncellulosic dialyzers. There was, however, a statistically significant difference in lymphopenia between the cellulosic and both noncellulosic membranes at 7.5, 15, 30 and 60 min ($p \leqslant 0.003$).

pH

Figure 5 is a composite showing the fractional change in pH for the three dialyzers with dialysis time. All changes in pH were small (less than 1% of initial value). There was an initial, small decrease in pH from the predialysis value to a broad minimum at about 30 min, followed by a gradual rise above the predialysis level. There was no statistically significant difference between dialyzers except at 180 min when the pH is higher for the PMMA dialyzer ($p = 0.02$).

PCO_2

The results of the PCO_2 with time of dialysis for each dialyzer are shown in figure 6. After an initial, small rise in PCO_2 with the onset of dialysis, there was a gradual steady decrease. The change in PCO_2 as with pH appears to be greatest with the PMMA membrane. However, except for the 180-min value ($p = 0.03$), the difference between the PCO_2 of patients on different dialyzers is not statistically significant.

Bicarbonate

The plasma bicarbonate level, calculated from the measured total CO_2 and PCO_2 according to the equation:

$$\text{Bicarbonate} = \text{total } CO_2 - 0.03\ PCO_2$$

is shown in figure 7. The bicarbonate level decreases rapidly with the onset of dialysis to approximately 95% of its predialysis value and remains at that level until 180 min. There was no significant difference between the different dialyzers in the trend or the extent of the change in plasma bicarbonate.

Discussion

The results outlined above show clearly a relationship between the extent of the hypoxemia and leukopenia and the type of membrane used in hemodialysis. These differences in biocompatibility between cellulosic and noncellulosic materials may have important clinical and therapeutic consequences in the dialysis treatment, and certain adverse effects which are common to most artificial kidneys in clinical use may be less severe or may not occur when patients are treated with artificial kidneys manufactured with noncellulosic membranes.

Increasing evidence suggests that dialysis-related hypoxemia has important clinical correlates, even in patients with apparently normal cardiopulmonary function. In a study of 8 dialysis patients with normal cardiac function, *Chen* et al. [21] found that dialysis patients breathing room air experienced dialysis-related hypoxemia and in these patients the systolic blood pressure fell by 17 ± 3 mm Hg at 15 min and by 30 ± 13 mm Hg at 120 min with no significant compensatory changes in heart rate or cardiac contractility. When hypoxemia was prevented by administering 40% O_2 by mask, no significant change in blood pressure occurred and heart rate and myocardial contractility increased. Thus, compensatory mechanisms that tend to counteract hypotension appear to be blunted with hypoxemia.

Dialysis-induced leukopenia is also associated with functional changes of neutrophils, such as chemotaxis [22,23], phagocytic ability, decreased random mobility [24,25] and increased adherence [26]. The rebound leukocytosis that occurs following the acute leukopenia has been shown to be partly due to the release of neutrophils from the bone marrow [3,27]. These newly released neutrophils also show decreased adherence [25].

Although there has been no demonstration that these laboratory studies of WBC function have adverse clinical correlates, it is well known that granulocyte adherence, chemotactic and phagocytic activities are essential mechanisms in the complex process for combating infection [28,29]. The cyclical variation of the number and function of neutrophils with each dialysis, and the decreased chemotactic responsiveness of neutrophils in dialysis patients may well contribute to some degree to the high rate of infection of hemodialysis patients [30]. Finally, a crossover study of 8 patients [31] has shown that the average predialysis WBC during hemodialysis with a cuprophane membrane dialyzer was lower than when patients were treated with a PAN membrane dialyzer.

The relationship, if any, between hypoxemia and leukopenia has been the subject of debate. *Sherlock* et al. [6] have suggested that alveolar hypoventilation due to the loss of carbon dioxide (as CO_2 gas or as bicarbonate) across the dialysis membrane was the cause of hypoxemia and that the leukopenia and hypoxemia are unrelated. However, the data of *Tolchin* et al. [16] and our own preliminary data suggest that there is still a drop in PO_2 in the first hour of treatment using bicarbonate dialysate, when there was a net transfer of CO_2 into, not out of, the patient.

More recent studies [11,12] also purported to show the lack of correlation between the leukopenia and hypoxemia induced by different membranes, and by comparing the degree of neutropenia and hypoxemia during isolated ultrafiltration and dialysis. However, in both studies, the parameters PO_2 and WBC were measured at times different from the maximum neutropenia (approximately 15 min and the maximum hypoxemia (approximately 60 min postdialysis) and therefore may not have shown differences between different membranes. In addition, comparison of changes in PO_2 and WBC during isolated ultrafiltration and hemodialysis is not strictly valid since these two different processes result in different hemodynamic changes [32] and rapid removal of large quantities of excess interstitial lung fluid during isolated ultrafiltration may be enough to mask any adverse effects of pulmonary WBC sequestration [33]. Of particular interest is the report that patients who are mechanically ventilated and therefore cannot hypoventilate also show hypoxemia during dialysis with cellulosic membranes [34].

Craddock et al. [4,9] on the other hand have attributed the hypoxemia to intrapulmonary complement-mediated leukostasis resulting in ventilation-perfusion mismatch. Animal studies with infusion of autologous cellophane-incubated plasma (with no extracorporeal circulation) clearly showed hypoxemia associated with leukopenia, and histologic examination showed intravascular pulmonary leukostasis. Other studies [35,36] have shown correlations between the changes in total WBC and arterial PO_2, a significant decrease in carbon monoxide diffusion coefficient in the lungs, as well as evidence for pulmonary

shunts during diaylsis. Animals dialyzed with cellulosic membranes experienced a significant rise in pulmonary artery pressure associated with the development of leukopenia, while dialysis with PAN membranes showed no such rise [37].

The results reported herein demonstrate clearly that the severity of the hypoxemia in the early phase (approximately 1 h) of dialysis depends on the nature of the membrane material used to manufacture artificial kidneys. This study also suggests an association between the hypoxemia and leukopenia of different dialysis membranes during the early phase of dialysis.

It is important to note that changes in PCO_2, pH and bicarbonate did not show significant differences between the types of membranes used. Furthermore, preliminary measurements of the mass transfer of PCO_2 and bicarbonate into the dialysate did not show any significant differences between different dialysis membranes. Thus, it is unlikely that the difference in the hypoxemia between membranes is due to differences in CO_2 diffusing capacity.

Studies of radioactively labeled neutrophils [3] showed that most or all of the original circulating neutrophils that were sequestered in the lung returned to the circulation after about one hour of initiation of dialysis. Thus, the persistent hypoxemia at later times during the dialysis, which was shown in this study to be independent of membrane material, cannot be accounted for by intrapulmonary leukostasis. Indeed, the resolution of the hypoxemia was associated with the resolution of leukopenia in the studies of *Craddock* et al. [9] on animals. The absence of this late-stage hypoxemia during bicarbonate dialysis [8, 16] suggests that this late-stage hypoxemia may be caused by dialysate-related factors; specifically, the loss of CO_2 and bicarbonate [38] and the metabolism of acetate from the dialysate [39] results in a significant reduction in CO_2 load that needs to be excreted by the lungs and consequently leads to hypoventilation and hypoxemia.

In summary, we postulate that the dialysis-associated hypoxemia is due to two concurrent processes. In the early stages of dialysis, i. e. first hour, the hypoxemia is related to the intrapulmonary leukostasis which in turn is strongly dependent on the membrane material being used. This is superimposed on hypoventilation-induced hypoxemia due to the reduction in the CO_2 load that occurs in acetate dialysis, which is independent of the membrane used and which persists after resolution of the pulmonary leukostasis. Both the hypoxemia and leukopenia may have important clinical implications, and the study of biocompatibility of membranes should be an integral part of dialyzer evaluation.

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Edmund G. Lowrie, MD,
1055 Commonwealth Avenue, Boston, MA 02215 (USA)