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Optimization of dialysis by membrane type

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Introduction

The choice of a dialysis membrane for a given patient influences uraemic toxin removal and also the degree to which the patient will be subjected to the problems of bioincompatibility. These in turn may influence the «adequacy of dialysis treatment» in its broadest sense and will influence morbidity and mortality. This argument will be developed in stages.

Adequacy of dialysis: definition

Adequate dialysis is not easy to define because there is no single toxin in uraemic sera for which levels correlate well with well being or outcome. It was long known that there is a poor correlation between toxin manifestations of uraemia and plasma concentrations of creatinine and urea. This discrepancy was most obvious in patients treated by longterm intermittent peritoneal dialysis who in spite of high creatinine and urea levels, appeared well and did not develop neuropathy. It was suggested that the peritoneal membrane was removing certain higher molecular weight substances more efficiently than the artificial membranes used in haemodialysis and that «leakier membranes» for the haemodialyzer were indicated. Interest in peptides of middle molecular weight (300-5000) developed and the «leakiness» of the peritoneal membrane to such middle molecules was confirmed. The observation that prolongation of dialysis time could arrest or reverse peripheral neuropathy independently of the pre-dialysis values for urea and creatinine form the background for the «square meter-hour hypothesis». This hypothesis related the efficiency of dialysis in preventing neuropathy to the weekley dialysis time and the active membranae surface area. Mathematical models were developed to predict the accumulation and transfer of middle molecules and it was suggested that a satisfactory clinical result attended a minimum weekley clearance of a hypothetical marker middle molecule represented by vitamin B_{12} (1355 daltons) of 30 l/wk/1.73 m^2.

Even without clear cut proof of the importance of these toxins, more permeable membranes were developed and dialyzers with larger surface areas were designed to enhance the removal of middle molecules. Similarly, the development of techniques such as haemoperfusion, haemofiltration and indeed continuous ambulatory peritoneal dialysis (CAPD) were based upon their favourable rates of removal of middle molecules.

Numerous attempts have been made to prove or disprove the middle molecule hypothesis. Various strategies have been designed to alter presumed levels of middle molecules both in body fluids and relate these changes to the symptomatology of a patient or to the in vitro toxicity of plasma or dialysate. Some of the results appear to support the hypothesis while others do not [1-3].

In spite of all of the enthusiasm for middle molecules, many doubted that they were any more important than small molecules in determining adequacy of dialysis. This controversy was addressed in the National Cooperative Dialysis Study (NCDS) which showed that patients with a high protein catabolic rate (PCR, g/kg/day) and also patients with a low blood urea nitrogen had low morbidity [4]. Thus, the dialysis prescription which achieves the lowest urea concentration with the best nutritional status should be sought in all patients. While the study clearly supported the importance of small molecules, treatment time (and presumably middle molecule removal) appear to have some influence on the morbidity rate as patients with high urea levels and short time dialysis, fared the worst.

The adequacy of a single dialysis

The biochemical changes that occur during a single dialysis depend upon several factors. At any point, the serum concentration of the substance depends on its rate of generation, volume or distribution, residual renal function, clearance of the haemodialyzer membrane and the elapsed dialyzer time. Clearance of the dialyzer will vary with the nature of the membrane,

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its effective surface area and the blood and dialysis flow rates.

The normalized «dose» of dialysis can be expressed by the value Kt/V where K = dialyzer clearance (ml/min) of a solute; t = time (minutes); and V = volume of distribution of the solute (ml). Gotch and Sargent [5] recently re-examined the NCDS data by mechanistic analysis. They show that the probability of uraemic manifestations developing was high (57 %) and the constant over the treatment range $0.4 < Kt/V < 0.8$; there is a sharp decrease in this morbidity to 13 % with increasing Kt/V which becomes constant over the treatment range $0.9 < Kt/V < 1.5$. They demonstrated that the mid week pre-dialysis BUN PCR and Kt/V are mathematically interrelated and the results of the NCDS could be depicted on a three variable plot (fig. 1) which shows areas depicting the high (triangular) and low (pentagonal) probability of development of uraemic manifestations. It is clear from this fiure that BUN (or urea) alone provides no indication for the level of treatment or the probability of morbidity and that all three parameters (BUN, PCR, and Kt/V) are required to describe adequacy of dialysis.

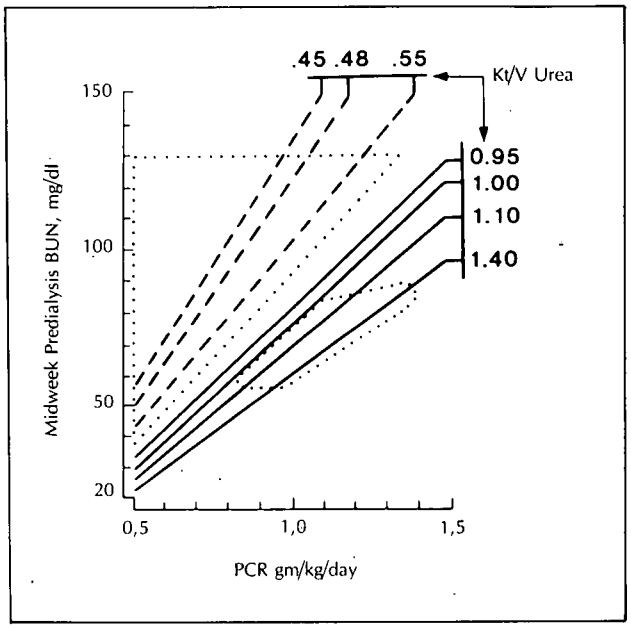

Fig. 1.—The interrelationship between midweek predialysis BUN, PCR, and Kt/V (urea) is shown together with the morbidity data from the NCDS. The triangular area depicts the domain of high probability of uraemic manifestions; the pentagonal area the domain of adequate dialysis.

The dependence of protein catabolic rate upon Kt/V (urea): The importance of nutrition

In a recent study by the author [6], urea kinetic modelling was performed serially over a two year period on a large number of patients undergoing both haemodialysis and peritoneal dialysis. The data obtained sugests that in dialysed uraemic patients who do not have extraneous factors eg. malignant or other disease of the gastrointestinal tract, the PCR (g/kg/day) is directly dependent upon the amount and type of dialysis treatment they receive as measured by the Kt/V (urea). The PCR as obtained from urea kinetic modelling is an excellent indication of patients' dietary protein intake (DPI) and hence, of appetite. Observations made on patients with low PCR's and DPI's receiving inadequate dialysis by NCDS standards showed that in spite of excessive dietary counselling and the provision of oral protein supplements, the patients would not eat until a more adequate dose of dialysis was prescribed. This together with observations that decreases in the Kt/V (urea) was also associated with downward modulation of appetite indicates the dependence of PCR upon the Kt/V (urea). The data otherwise might be interpreted as a reflection of the increased dose of dialysis (Kt/V) necessary to control the urea of patients ingesting larger quantities of protein. The relationship between PCR and Kt/V (urea) for all patients on haemodialysis is shown in figure 2. These observations led to the formulation of a hypothesis which stated that NCDS data may be reinterpreted as follows: The major determinant of mortality is the nutritional status of the patient as indicated by the PCR: a PCR $\geq$ 1 g/kg/day cannot be obtained without adequate dialysis as indicated by Kt/V (urea) $\geq$ 1 for cellulosic membranes. If such adequate dialysis has been prescribed, then the plasma urea level is controlled and does not per se have direct influence on the outcome. In this regard, the study of Kupin et al. [7] showed the greatest influence on low morbidity in haemodialysis patients, was the maintenance of a PCR between 1.1 and 1.4 g/kg/day. The study of Acchiardo et al. [8] also showed the influence of PCR on outcome which appeared independent of the BUN level: in fact the group with the best outcome statistically had the highest pre-dialysis values.

A second hypothesis generated from these studies is that different treatment methods influence the interrelationship of PCR and Kt/V (urea) in different ways. The data suggested that to obtain a PCR of 1 g/kg/day a Kt/V (urea) of 1 must be prescribed when using cellulosic dialysis membranes (fig. 3). This is an excellent agreement with Gotch's mechanistic analysis of the NCDS [5]. Should a PCR of 1.4 g/kg be felt to give added protection from morbidity (currently there is no data to support this) then a Kt/V (urea) of 1.6 would be necessary for the cellulosic membrane. The use of the more permeable and bio-compatible polyacronytrile membrane (AN69S) as in the HOSPAL (Basle, Switzerland) series of dialyzers should provide the

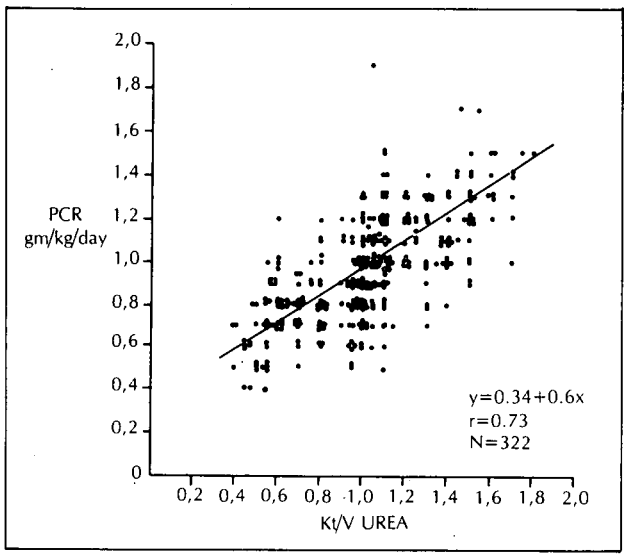

Fig. 2.—Plots of PCR v Kt/V (urea) for all haemodialysis patients.

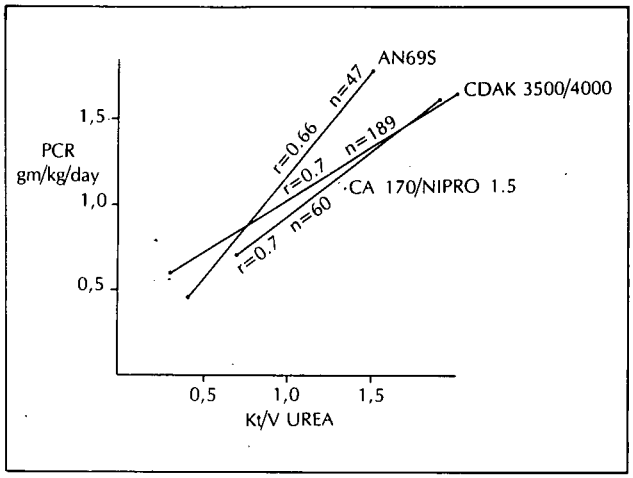

Fig. 3.—Regression lines of data points of PCR v Kt/V (urea) for patients dialyzed by different haemodialyzers.

patient with a PCR of 1 g/kg/day if a Kt/V (urea) of 0.8 is given. If the higher PCR of 1.4 is desired, then the Kt/V (urea) must be 1.19. In other words, a lower dose of dialysis as modelled by urea is necessary for the same influence on PCR as a given dose using the cellulosic membrane. Support for this hypothesis comes from a crossover study of cellulosic vs. AN69S dialysis in which patients were modelled while on the cellulosic membrane and their time average concentration (TAC) urea levels were calculated. The blood flow rates and other conditions of dialysis using AN69S membrane were then set to maintain the same TAC (urea). In spite of this, after two months on dialysis by AN69S there was a significant elevation in the mid week pre-dialysis urea value. Originally it was felt that the K value used to model the AN69S containing dialyzers was inaccurate but subsequent review of the data showed that these patients had increased DP's while receiving experimental therapy [9].

Explanations for this are possible: the most obvious relates to the different solute clearance profiles that exist with dialysis by AN69S and cellulosic membranes. Thus, removal of equal amounts of urea by these membranes will be associated with a greater removal of higher molecular weight, retention products by the more permeable AN69S membrane [11, 12].

Bio-compatibility, dialysis symptomatology and their influence on adequacy

Dialysis induced leucopenia during the first ten to twenty minutes of routine haemodialysis with cellulosic membranes is well known. Craddock et al. [13] were the first to show that this phenomenon was associated with the activation of the complement system leading levels by releasing heir constituents and aggregating together; the aggregates become trapped in the pulmonary microvasculature resulting in ventilation perfusion mismatch and hypoxemia. Craddock at this early stage suggested that these phenomena may be associated with symptoms such as dyspnea, chest pain and back pain that may occur during the early course of cellulosic dialysis. Other workers were quick to see that haemodialysis with membranes of different chemical composition resulted in varying degrees of complement activation and leucopenia; the AN69S membrane causing reduction in these phenomena as compared with the cellulosic [14]. Further studies carried out by the author using an animal model have shown that the contact of blood with dialysis membranes will activate the complement system with the generation of biologically active analphatoxin C5a which in turn stimulates the pulmonary endothelium to release vasoconstrictor thromboxane A2 which then increases the pulmonary vascular resistance and causes pulmonary hypertension. Should very severe pulmonary hypertension occur, right heart dysfunction follows. This may be associated with a fall in the cardiac output, myocardial ischemia and cardiac arrhythmias. It was found that the hypoxemia was not due, as Craddock thought [13] to the pulmonary leukostasis but rather to the events as outlined above for sheep rendered leucopenic following nitrogen mustard therapy also developed acute pulmonary hypertension and serial lung biopsies in healthy sheep demonstrated that pulmonary leukostasis occurred several minutes after the humeral events and the development of hypoxemia [15]. Other workers have confirmed this sequence of events in sheep, dogs, and in the pig. In

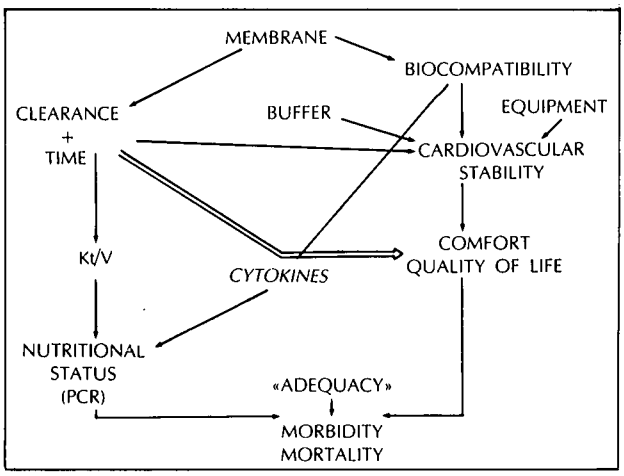

Fig. 4.—Systematic diagram showing factors involved in the effect of membrane choice on outcome.

Table I. Comparison of haemodialyzers

Dialyzer type	Relative values % *		Sheep ** Δ mean PAP mmHg
	C3a	Leuko-penia	
Cuprophane	100	100	30
Cellulose acetate (CDAK)	67	43	20
Hemophan	60	62	21
Cellulose acetate (CA70/CA90)	48	22	17
Polycarbonate	40	53	No data
Polysulfone (F60)	24	12	2
Reused cuprophane (saline formalin)	15	38	0
PAN (Hospal)	5	0	5

* Data from Henderson and Chenowith [18].
** Data from Lindsay [15].

the latter animal, Cheung [16] infused C5a and acute pulmonary hypertension occurred rapidly.

Extrapolating such data from animal to man is difficult. Nevertheless, many of the symptoms of «dialyzer hypersensitivity» as described in the literature, indicated a disturbance of the cardiopulmonary circulation. It is the author's contention that many of the cases of «dialyzer hypersensitivity» syndrome represent the severe end of a spectrum of phenomena; at the benign end of the spectrum is the occurrence of hypoxemia and neutropenia in asymptomatic patients. The fact that more pronounced changes are found in sheep then in humans, represent species sensitivity difference. There is supportive evidence for this hypothesis in man. The author's group studied patients undergoing cellulosic haemodialysis for acute renal failure: Changes in pulmonary vascular tone occurred in the first fifteen minutes of haemodialysis; these ranged from increases in calculated pulmonary vascular resistance index to the development of frank pulmonary hypertension. It was also observed that this pulmonary vascular response coincided with C3a generation and with peripheral leucopenia [17]. It is likely therefore, that the range of symptoms experienced during clinical dialysis from minor degrees of chest pain and hypotension (which are very common) to the rare but severe symptoms characteristic of «dialyser hypersensitivity» might reflect the spectrum of acute pulmonary hypertension produced. The severity of this cardio-pulmonary response will likely vary with the nature of the surfaces used, with the amount of plasma factors produced by the blood foreign surface interaction, with the sensitivity of the pulmonary vascular bed to these factors, with the presence of antagonists (eg. drugs) and with the presence of any intercurrent dysfunction of the cardiopulmonary circulation.

While the link between intravascular complement activation and dialysis related symptomatology and morbidity is not strong, complement activation nevertheless has become one of the hallmarks of bio-compatibility studies. Henderson and Chenowith [18] examined the complement activation potential of haemodialyzers using an in vitro perfusion circuit. Their study suggest a rough subdivision of membranes to three broad categories is possible and may be useful clinically. Results of these dialyser studies are summarized in table I. In all cases, the C3a antigen production and the leucopenic response obtained during the initial 30 minutes of dialysis has been normalized to similar responses produced by a dialyzer containing cellulosic membranes manufactured by the cupra-ammonium process (Cuprophan). Membranes that display minimal complement activation and leucopenia, for example, PAN (AN69S), polysulphone and saline rinsed/formalin stored re-used Cuprophan constitute one group, there is a second «intermediate activity» group compromised of dialysers containing membranes of cellulose acetate and polycarbonate and there are those that fall into the third «most active» category which resemble the response of those containing Cuprophan. What is extremely interesting is that there is almost a direct correlation between this grouping and the results obtained in the sheep model using the degree of pulmonary hypertension produced as the end-point (table I).

Again, there may be arguments to the relevance these observations are to the generalized discomfort of dialysis therapy. However, studies using psychometrics for dialysis related symptoms as part of the measurement of «quality of life» in multi-centre dialysis related studies show that bio-compatibility is important (Lindsay RM and Burton HJ; in progress). The

importance of adverse dialysis related symptoms on the long-term «adequacy of dialysis» has been questioned. Data from the Ontario «Adaptation to Home Dialysis Study» [19] clearly has shown that psychosocial factors are of equal importance to pathophysiological events in determining morbidity and mortality, success and failure, and are of major importance in determining quality of life [20, 21]. A psychometric test developed for this study is the treatment regimen stress scale (TRS) [20, 21] which reflects the stress related to the dialysis therapy.

A high TRS score has been found to be the most important cause of failure from home haemodialysis programs and correlates with depression (as measured by another tool) which in turn is an important independent determinant of living or dying [21] on dialysis programs. It is therefore, extremely important to make dialysis more comfortable and thus the newer techniques of dialysis involving the more bio-compatible synthetic membranes, biocarbonate buffer, and volumetric control systems are likely to significantly influence outcome.

Returning again to bio- compatibility while the complement system has been a primary focus clearly other systems are involved; the most interesting currently is that related to interleukin 1 (IL-1). It has been known for years that the human host responds to infectious, toxic, inflammatory and immunological challenges with a remarkably consistent set of changes that are grouped together and called «the acute phase response». This response includes amongst other things, tissue catabolism. The haemodialysis procedure has been shown to induce IL-1 production and is a catabolic event [22]. Therefore, biocompatibility (or lack of it) may influence the nutritional problems of dialysis and therefore, morbidity and mortality. There is already evidence that dialysis by a synthetic biocompatible membrane is less catabolic than that using cellulosics (Bergström), personal communication).

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References

1. Henderson LW: Middle molecules re-examined. *Nephron* 22:146-152, 1978.
2. Bergstrom J, Furst P and Zimmerman L: Uremic middle molecules exist and are biologically active. *Clin Nephrol* 11:229-238, 1979.
3. Bergstrom J and Furst P: Uremic toxins. In Drukker W, Parson FM and Maher JF (Eds.): *Replacement of Renal Function by Dialysis* (2nd ed.). New York, Martinus Nijhoff Publishers, chap. 19, pp. 354-390, 1983.
4. Laird NM, Berkey CS and Lowrie FG: Modelling success or failure of dialysis therapy. The National Cooperative Dialysis Study. *Kidney Int* 23 (suppl. 13):S101-S106, 1983.
5. Gotch FA and Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28:526-534, 1985.
6. Lindsay RM and Spanner E: A Hypothesis: The protein catabolic rate is dependent upon the type and amount of treatment in dialyzed uremic patients. *Am J Kid Dis* vol. XIII. 5 (May):382-389, 1989.
7. Kupin W, Zasuwa G, Kilates MC et al.: Protein catabolic rate (PCR) as predictor of survival in chronic hemodialysis patients. *Council Renal Nutr Q J* 10:15-17, 1986.
8. Acchiardo SR, Moore LW and Latour PA: Malnutrition as the main factor in morbidity and mortality of dialysis patients. *Kidney Int* 24 (suppl. 16):S199-S203, 1983.
9. Lindsay RM, Burton HG and Heidenheim P: An evaluation of the Hospital dialysis system and its role in safely reducing dialysis time: A pilot study. A report to Hospal Ltd., Basle, Switzerland. *UWO Press* 1-43, 1986.
10. Lindsay RM and Henderson LW: Adequacy of dialysis. *Kidney International* 33 (suppl. 24):S92-S99, 1988.
11. Bergström J, Alvestrand A and Gutiérrez A: Acute and chronic metabolic effects of hemodialysis. In Smeby LC, Jorstad S and Wideroe TE (Eds.): *Proceedings of the International Symposium on Immune and Metabolic Aspects of Therapeutic Blood Purification Systems.* Trondheim, Norway, pp. 254-273, 1985.
12. Shaldon S: Future trends in biocompatibility aspects of hemodialysis and related therapies. *Clin Nephrol* 26 (suppl. 1):S13-S16, 1986.
13. Craddock PR, Fehr J, Brigham KL, Kronenberg RS and Jacob HS: Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. *N Engl J Med* 296:760-774, 1977.
14. Hakim RM and Lowrie EG: Hemodialysis associated neutropenia and hypoxemia: The effect of dialyzer membrane materials. *Nephron* 32:32-39, 1982.
15. Walker JF, Lindsay RM, Peters SD, Sibbald WJ and Linton AL: A sheep model to examine the cardiopulmonary manifestations of blood-dialyzer interactions. *ASAIO J* 6(3):123-130, 1983.
16. Cheung AK: Animal models to study the cardiopulmonary effects of artificial kidney membranes. *Blood Purification* 5:155-161, 1987.
17. Walker JF, Lindsay RM, Sibbald WJ and Linton AL: Changes in pulmonary vascular tone during early hemodialysis. *ASAIO Transactions* 30:168, 1984.
18. Henderson L and Chenoweth D: Bio-compatibility of artificial organs: An overview. *Blood Purification* 5:100-111, 1987.
19. Burton HJ, Canzona LK, Lindsay RM and Palmer S: Adaptation to home dialysis: the Ontario experience, Final report. London, Ontario, Canada, UWO Press, 1985.
20. Richmond JM, Lindsay RM, Burton JH, Conley J and Wai L: Psychological and physiological factors predicting the outcome on home hemodialysis. *Clin Nephrol* 17(3):109-113, 1982.
21. Wai L, Richmond J, Burton H and Lindsay RM: The influence of psychosocial factors on survival of home dialysis patients. *Lancet* 2:1155-1156, 1981.
22. Dinarello CA: The biology of Interleukin I and its relevance to hemodialysis. *Blood Purif* 1:197-224, 1983.
23. Lowrie E: NMC Mortality Study. Presented at American Society of Nephrology, Washington, DC, USA, December 1989 (unpublished).