PART II

GUEST LECTURES ON HAEMODIALYSIS

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DIALYSIS MEMBRANES

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The essential function of an artificial kidney is the extraction of selected metabolites from blood across a blood-wetted surface. Occasionally the surface has been a sorbent particle in which case it is necessary for the medium to exhibit both selectivity and capacity to store metabolites. In almost all clinical situations the surface is that of a membrane, in which case capacity is irrelevant. Three aspects of a membrane determine its suitability:

1. Its spectrum of transmission coefficients. In haemodialysis these are the diffusive permeabilities of the solutes and the hydraulic permeability of the solvent, water [1]. In haemofiltration the important coefficients are, for the solvent, again the hydraulic permeability and for the solutes the product of this permeability by each solute’s ‘sieving coefficient’ [1,2]. Some devices and treatment strategies are mixed in that solute transport is determined by both kinds of transmission coefficients.

2. The practical burdens it places on the system and thence the patient and physician.

3. The absence of negative effects on the patient’s well-being: its biocompatibilities.

In this paper an assessment according to these aspects of membranes in current artificial kidney devices is presented. The principal purpose is to identify the further developments that are likely and to determine whether they are those that are most desirable. It is concluded that important changes in the qualitative and quantitative aspects of transport properties are not mandated by defined medical needs and will not occur; that cost will continue to dominate membrane development and patterns of membrane use, including re-use; that efforts should and will continue to remove bioincompatibilities, but only within rather strict limits imposed by costs, and that variegated therapeutic approaches will be more commonly specified to limit special membranes and devices along with the costs they carry to patients and situations that require them.
Transmission coefficients (diffusive and hydraulic permeabilities, sieving coefficients)

A finite transmission coefficient causes solute movement only if a driving force is present. The driving force of dialysis is a difference between the chemical activity of the solute in plasma and in dialysate. For most, but not all, solutes this difference is well approximated by a difference between plasma and dialysate concentration. The principal exceptions are substances that exist in multiple forms, e.g. free and bound calcium, multivalent anions such as the phosphates, and small molecules that bind significantly to larger ones such as proteins. The driving force of haemofiltration is a difference in pressure across the membrane. It is very important to remember that for clinical situations one must consider a spectrum of transmission coefficients. The luxury of designing a membrane to deal optimally with one substance without regard for how it behaves with other substances is not permissible. No artificial kidney membrane — nor that of any dialyser, haemofilter, or even the peritoneum — has an appropriate spectrum of transmission coefficients, and it is thus necessary to compensate for the inappropriate spectrum. The procedure is universal: find a membrane and use enough of it to remove a sufficient amount of the substance most difficultly removed, using a maximum driving force. For dialysis this driving force will be the plasma concentration minus the minimum concentration of substance attainable in dialysate, essentially zero. Then compensate for the excessive amounts that would be removed of other substances by setting finite, non-zero concentrations of these substances in the dialysate, thus decreasing their driving forces. Following this universal approach leaves one with a more-or-less expensive solution that moderates the permeabilities of dialysis or compensates for the excessive values of the product of hydraulic permeability by sieving coefficient in haemofiltration.

It is interesting to divide all metabolites into five categories in order to examine the spectrum of transmission coefficients. These are:

1. The solvent water
2. The major (‘stoichiometric’) bearer of nitrogen, urea
3. The small, ionised species
4. The ‘middle molecules’, both those one wishes to remove and those one wishes to retain
5. Large molecules.

Given the few parameters adjustable in any given membrane system the approach to achieving a spectrum that is workable — albeit only with the driving force compensation just described — has been to stipulate urea as the substance whose quantity and transmission coefficient considered together define it to be the substance most difficult to remove and then to maximise the coefficient for urea subject to maintaining the large molecule transmission at essentially zero. In dialysis, maximisation of urea permeability has almost always set the hydraulic permeability to water in a range where water movement could be controlled by adjusting the transmembrane pressure. (However, in a few cases
an upper limit on hydraulic permeability has been the factor limiting how high urea permeability could be raised because of technical difficulty in maintaining transmembrane pressure near zero.) With urea permeability sufficiently high, permeability to salts has been high enough that their movement could be controlled by decreasing ionic driving forces through the addition of salts to dialysate. In some instances phosphate becomes an exception to this generalisation, and aluminium has been described as an exception although, in fact, its transport is controlled not by its permeability but by concentrations in dialysate that are small but significantly different from zero. After many years of research, agreement still remains to be reached on the importance of removing any middle molecules larger than creatinine and uric acid [3].

It is clear that the use of pressure as a driving force in haemofiltration gives rise to a spectrum of effective permeabilities different from that achieved in dialysis and, for some patients, a consequent clinical improvement. The theory of diffusion in membranes shows that for a given membrane the decrease in product of hydraulic permeability by sieving coefficient that occurs with increasing molecular weight will occur rather more sharply at higher molecular weights in comparison to the steady changes in diffusive permeability that take place over a wider range of molecular weights. However, both for dialysis and for haemofiltration, the concept of a ‘cut-off molecular weight’ that separates solutes that will pass a membrane from those that will not is a vast over-simplification. Figure 1 is a sketch showing qualitatively how one might expect the diffusive permeability and the product of hydraulic permeability by sieving coefficient to vary with solute molecular weight for a series of chemically similar, penetrating solutes. The figure is based upon approximate calculations using the data of reference 4.

Many commentators have wished for haemodialysis membranes in which the entire spectrum of molecular weights was raised so that less membrane area would be required to cause a given removal rate. Developments in this direction have been principally physical, that is the membranes have been made more permeable not by changing their chemical composition and thus their intrinsic diffusive properties, but rather by decreasing their thickness. Thus far these overall improvements in membrane permeability have been beneficial to designers who understood them and adjusted appropriately the configuration of the devices using the more permeable membranes. However, substantial further progress may not be possible. Here is the problem: higher permeabilities are useful only if employed to increase the rate of solute removal per unit of dialyser area, the so-called solute flux. If membrane permeabilities are increased to allow higher solute fluxes one must either arrange also to improve transport coefficients in the adjacent blood and dialysate (especially the former) or one must expect that conditions in these fluids will increasingly take control of the permeability spectrum away from the membrane. The permeability spectrum of contemporary membranes, even though imperfect, is far more desirable than that which transport controlled by blood, alone, would dictate. Transport coefficients in blood can be increased to avoid this problem, but only by increasing, through design changes, the shear rate of the blood [5]
Figure 1. The logarithm of transmission coefficient is plotted versus the logarithm of molecular weight for a series of polyethylene glycol molecules acting as solutes passing through a membrane of polyvinyl alcohol [4]. The upper data set is calculated from the lower set by dividing the respective points by a factor proportional to the free-liquid diffusivity of each solute molecule; they and the line fitting them represent the sieving coefficient one would expect to observe with this membrane. The lower set of points are obtained directly from measured data and, with the line drawn through them, give the diffusive permeability as a function of solute molecular weight. If the 'cut-off' is defined as the transmission coefficient that is half that for a small molecule, the value for the sieving coefficient is about 460 while that for the diffusive permeability is about 250.

and thus, as a necessary consequence, the blood-side pressure drop. Increasing the pressure drop may lead to excessive ultrafiltration unless the hydraulic permeability is lowered. Thus the desiderata of membrane design, even considered only with respect to transport, are several and probably conflicting at the level of membrane design. To repeat, substantial further improvement in the overall permeability of dialysis membranes is unlikely. It is also unlikely that the shape of the membrane permeability spectrum (viewed, say, as a plot of permeability versus solute molecular weight) will be significantly changed in the foreseeable
future. There is not a clear enough goal to be addressed by doing so, especially since other aspects of membranes, considered below, deserve more attention.

The practical burdens a membrane imposes

The practical burdens imposed by a membrane are not widely recognised, but they are very real.

Associated with every membrane is a direct cost: the price of the membrane itself. Also associated with every membrane are hidden costs: these include the design features necessary to hold it in proper contact with the blood stream. For example, some membranes cannot be well formed as hollow fibres; the requirement of using them in a more expensive flat-plate configuration is a hidden cost. As already mentioned, dialysing or replacement solution is used to compensate for the imperfect aspects of a membrane’s permeability spectrum; the price of this solution is also a hidden cost. Some membranes may require the use of greater quantities of drugs or the use of more time and materials at the clinic to prepare them (e.g. by rinsing); these materials and procedures generate other hidden costs. The true cost of a membrane is the sum of its direct and hidden costs. This cost will not be the same everywhere because it depends not only on the economy of the factory, but also on the value assigned to the patient’s time loss during treatment and the value ascribed to labour in the clinic. Calculating this cost must include taking account of the pressure that may or may not exist to give other responsibilities than dialyser preparation to clinical staff. These observations are particularly true and their consequences particularly difficult to assess when dialyser re-use is considered. The direct membrane cost per dialysis is clearly reduced by re-use. The effect of re-use on true cost depends enormously on complex calculations involving the perceived cost and availability of labour and the availability and cost of capital to automate re-use when labour cost is an issue. These factors vary greatly from area to area, among kinds of institutions within a given area, and sometimes even among different clinics in the same institution.

It is perfectly clear that the true cost of a membrane will be the major factor that determines the degree to which it is accepted — when the situation is observed over a long period of time. Over a shorter period of time, other considerations such as technical novelty, the ability of a membrane to address a particular medical problem that is of concern at one time, the role of nationalism and other, political, non-economic forces at work in the market place will all exert a force. However, only one factor will remain as important as true cost for any membrane that has a basically acceptable permeability spectrum. This factor has acquired a very fancy name over the past few years: biocompatibility. Except for a few summarising remarks, the balance of this paper will be devoted to a consideration of this aspect of membranes. Consideration will be given to the quality of biocompatibility as it applies not only to membranes but also, necessarily for the purposes of this article, to whole artificial kidney systems.
Biocompatibility and Bioincompatibility

It is impossible to consider ‘biocompatibility’ in any reasonable technical detail as it would be so to consider ‘health’. Biocompatibility can only be reached by eliminating recognised bio-IN-compatibilities just as health can only be reached by focusing attacks on particular diseases. In artificial kidney systems, bio-incompatibilities can arise from any of the following components: in the dialyser — membrane, case material, potting compound, and dialysate; in the rest of the system — tubing, needles, and injectables. The great emphasis placed upon the bioincompatibility of membranes in contrast to the rest of the dialysis system arises because many deleterious phenomena depend upon area, and the area of contact between blood and membrane far exceeds that of any other component of an artificial kidney. Each source of bioincompatibility must be examined for the principal mechanisms by which it may do damage. These sources are: leaching, protein transformation at the interface, cell adhesion and aggregation, and mechanical (shear) effects [6].

*Leaching* is the slow dissolution of some entity from a solid phase into surrounding liquid. It is a major potential mechanism of bioincompatibility. Membranes have been suspected of leaching oligomer [7] (low-molecular-weight fractions of the membrane-forming polymer), sterilants such as ethylene oxide [8] and formaldehyde [9,10], and trace contaminants both organic and inorganic. In addition to acting as a possible source of contamination itself, the membrane determines what potential contaminants from dialysate may reach blood. Studies have repeatedly shown that the membranes commonly used block the passage of organisms and neither serve as the source of, nor allow the passage of, endotoxins [11,12]. Looking beyond membranes, leaching of phthalate esters from tubing [13] has also been reported, to a degree that may have long-term significance for patient health. By some stretching of the definition, one may include under leaching the release of *particulate matter* into blood. Such matter may be particles inadvertently introduced into a device at the time of manufacture or may be products of mechanical degradation occurring during processing, storage, or use of any part of the system. The particulates that have attracted greatest attention are fragments detached from the tubing segment of a roller pump [14,15]. Particulates are also potentially (and actually) present in all parenteral solutions and all injected drugs.

*By protein transformation* is meant the heterogeneous chemical reaction of a plasma protein at a surface so that the product has changed biological activity. The major transformations that have been recognised so far are activation of clotting factors [16,17] and complement [18]. Activation may lead to clinically significant events that occur either at the activating surface (when the activated substance remains adsorbed), at a distal point in the system, or in the bulk, systemic blood. Studies of activation are difficult because clinically recognisable effects vary widely, even when activation may be occurring at the same rate; this variability arises because clinically observable phenomena probably involve overload of a compensating mechanism in the patient. When activation rate exceeds capacity for deactivation, which may vary substantially from
patient to patient and even from day to day in the same patient, clinical symptoms build rapidly. Below this threshold they may be almost totally absent.

One of the most insidious bioincompatibilities to have been encountered in artificial kidneys is rare but life-threatening anaphylactic reaction consequent to initiation of dialysis. The phenomenon is still not well understood but may involve both leaching and protein transformation. It is suspected that ethylene oxide leaches from the mass of polyurethane potting compound used to immobilise membrane in many hollow-fibre dialysers. The ethylene oxide then transforms one or many plasma proteins or possibly some of the soluble oligomer in the membrane in such a way that a potent allergic reaction is induced in a small sub-population of all patients. It is clear that the dominant reservoir of ethylene oxide in dialysers following gas sterilisation is the potting compound [20]. A very similar physical problem exists with respect to the use of formaldehyde in dialyser re-use although the biological consequence is different. Studies - which are underway - are urgently needed to find the principal reservoirs for formaldehyde, perhaps so that dialysers that rinse more effectively can be designed specifically for re-use.

Cells are frequently involved in bioincompatibility phenomena. The clinically dominant effect may be either depletion of cells - e.g. leukopenia - or their activation followed by such non-physiological behaviour as adhesion to artificial surfaces, bulk aggregation, and sequestration in particular capillary beds [21–24]. The mechanism of cellular interaction may be direct - contact with a surface which affects the cell inherently or through some molecule (most likely a protein) absorbed upon it - or indirect. Indirect mechanisms include reaction of cells in bulk blood with proteins transformed at a surface and subsequently returned to the blood. Activated complement probably affects cells in this manner. However, the indirect mechanisms involving cells may be even more complex; some cells that interact directly with a surface may subsequently release substances into bulk blood so as to affect cells that never directly contact the surface. Both leucocytes and thrombocytes have this capability [25].

Separately and as a modifier of the phenomena described above, *mechanical effects* are also a cause of bioincompatibility. Two basic flow phenomena account for the great preponderance of mechanical effects. These are flow separation [26] and shear [27]. Flow separation occurs in rigid artificial systems that have abrupt shape changes. Its effect is to place a small part of a device's blood volume into relative isolation and sustained contact with a surface. This volume then becomes a small reactor whose contents interact without dilution and in intimate contact with an artificial surface for long periods of time. The damage arising from separated flows may be local, e.g. the formation of a thrombus in the separated region or it may be systemic: the separated flow can serve as a nidus from which systemic toxins are generated. The elimination of separated flows is a matter of engineering although it may not always be simple engineering.

Shear is an ignored and misappreciated phenomenon that occurs everywhere in flowing blood [28]. Shear is the sliding of fluid layers over one another. It has many effects. The simplest is the distorting force it exerts on a cell trapped between two layers. These forces can result in lysis but more often they result in sublethal cell damage that causes release of metabolites from a cell, initiation
of intracellular processes (like the combination of actin and myosin and the subsequent shape changes that occur in platelets), and increases in the tendency of cells to adhere and aggregate. Sometimes the potentiating of aggregability is temporarily concealed by the very shear that caused it. Sometimes it is only when the stresses that prevent two cells from staying next to each other long enough to adhere are removed, that the actual aggregation occurs [29,30]. Shear is greatest in fluid that is immediately adjacent to a surface. A cell that has adhered to such a surface will be more damaged by shear flow than it would be if it were free. The cell may be torn away from the surface, leaving a part of itself behind. Alternately, it may be provoked very quickly to empty itself of metabolites.

By far the largest shear levels encountered during haemodialysis occur in the arterial and venous cannulae [29]. In general the situation is worse in single-needle, single-lumen systems and worst of all in single-needle, double-lumen systems [30]. While the time of exposure is short in this part of the system the rates of shear may exceed 20,000 sec\(^{-1}\), perhaps 50 times that encountered in the juxta-membrane volumes within a dialyser. As already noted one does not see the effects of this shear in the needle but rather in distal, low-shear regions. If the dialyser operated at a low shear rate and with narrow spaces, the result will be extracorporeal deposition of cells; otherwise the cells may only manifest their damage intracorporeally.

Shear may also cause cells to tumble and thence to migrate, usually so as to create a cell-free zone near the wall. However, these processes may result in increased (rather than decreased) exposure of susceptible cells because it may be precisely they that are margined on the outer surface of the cellular core formed by migration.

The largest effect of shear, however, is upon the exchange of molecular species between a fluid and its bounding wall. The effect of shear on molecular exchange pertains primarily to the artificial kidney as an efficient transport device for metabolites (see above), and is not our present subject. However, the effect of shear on transport may also enhance or ameliorate an underlying bioincompatibility. Moderately high shear will cause more cells and molecules of blood to contact a reactive surface and may thus result in a more widespread effect of the bioincompatibility. This fact notwithstanding, it is more likely that the dominant effect of moderately high shear will be the dilution of reaction products and the control of local events such as thrombogenesis so that they do not eventually force shutdown of the system.

The pursuit of biocompatibility, like the pursuit of health is a complex matter, and probably an unending scientific Odyssey. The conquest of one problem only sets the stage for an attack upon the next. For example, in all the foregoing discussion, no mention has been made of the clinically mandatory use of heparin to overcome one of the most fundamental bioincompatibilities encountered in extracorporeal therapy: the activation of clotting. So long as systems require heparinisation — and it is systems, not membranes, that must be addressed — they can hardly be considered to be biocompatible. However this issue has as many economic as therapeutic overtones; elimination of the heparin requirement will save money and when it occurs will be strongly affected
not by a purely technical solution, which may already exist, but rather by whether the cost exceeds the saving. In like mode, elimination of complement activation, transient leukopenia, and pulmonary distress at the onset of dialysis (whether or not these phenomena are connected), will depend upon identification of a real and ultimately cost-related problem and upon discovery of a cost-effective modification of membranes, devices, or procedures to eliminate the real problem.

What, then, does the future hold for dialysis membranes? In the best of all possible worlds: variety. In the hands of membrane manufacturers such variety already exists. Economics, variations in a patient’s requirements, different perspectives in the world regarding the value of capital and labour, and the very process of continuing discovery in the research laboratory and the clinic demand that the users and choosers of dialysers not strive for the unique best, the monolithic solution. For example, the needs of developing countries will be addressed wholly differently from those where artificial kidney therapy is already established as a right. To give another example, in any area, there will be found patients and situations that require special devices and membranes, but there is no need to impose these on a whole patient population in order to provide what is necessary or highly desirable for only a few. Some members of society will embrace wholly portable artificial kidneys and one may expect to see effective devices of this type in use before the present decade has passed, but not for the majority of patients. Re-use has not yet become a settled, ensconced activity, and it is likely that manufacturers will offer disposable dialysers cheap enough that users in areas where the cost of capital and labour is explicitly considered will think twice before espousing re-use, at least if their principal motivation is economic. All these compelling reasons for a varied approach will place great responsibilities — as free choice always does — upon the clinical staff. Both the chances to mismatch, even tragically, and the chances to provide truly superior rehabilitation will be much enhanced.

Whether regenerated cellulose will continue to be the dominant membrane for haemodialysis will be decided, firstly, on the basis of its total cost per dialysis relative to other possible materials and, secondly, on its perceived biocompatibility relative to other materials, with the necessary proviso that as current research will change these perceptions and possible chemical modifications to both cellulose and competing materials may modify their reactions with biological molecules.

Perhaps the most exciting thing to be said about dialysis membranes in 1984 is that a simple prediction about them is impossible.

Acknowledgment

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References

4. Odian M, Leonard EF. Trans ASAIO 1968; 14: 19
11. Port FK, Berneck J. Contr Nephrol 1983; 36: 100
18. Chenoweth DE. ASAIO J 1984; 7: 44

Open Discussion

GOTCH (San Francisco) You indicated that there is now adequate technical knowledge to fabricate a non thrombogenic artificial kidney circuit. Would you please elaborate on this comment.

LEONARD I think the developments in Sweden by Drs Larssen, Olsen and their colleagues could be brought to the point where a totally heparin free dialysis could be effective. I think that most people here do not want a heparin free dialysis under the present conditions because of the burden it places on staff. You would end up taking care of a few patients without heparin rather than the large number of patients you could take care of with ‘automatic’ heparin.

DI GIULIO (Rome) What are the relationships between biocompatibility and the electrical charge of the dialysis membranes and what are the effects of the membrane electrical charge on ion transport?
fringe around it in the sense that people state that one aspect of the membrane determines its biocompatibility. The fact is that we have been unable to separate out the specific aspects of the membrane which determines its biocompatibility. If one chooses a particular system and then proceeds to alter the charge, paying attention to which ionic groups are placed on the membrane as the charges alter, one can get some kind of a biocompatibility correlation. We are very ignorant on this subject. If the biocompatibility is based on platelet adhesion we will get some kind of a ranking but if it is based on activation of factor XII we will get a different ranking and if it is based on complement activation or leucocyte adhesion we will get yet an even different ranking. In systemic studies we will find large variations from patient to patient because some patients will be near their leucocyte activation thresholds while others will be near their thrombocytopenia thresholds. I think we are simply not at a place where we can say, except for those with very simplistic view of life, the charge is separable as a factor.

As far as ion transport is concerned a probable rule of thumb is to make the membrane as neutral as possible because the moment one puts a charge on a membrane it does more to drive away the counter-ion than to induce the movement of the ion whose charge is on the membrane. In general if one wants to optimise the membrane for ion transfer at a given overall porosity the membrane should be as charge free as possible. The subject of specific ion transfer across membranes will be revisited but my guess is that what we will have will not be membranes that have better ion transfer but artificial kidneys with built in capacity to remove specific difficult ions such as phosphate by sorption. However I do not know of any developments in this field as yet.

PORT (Ann Arbor, Michigan) You have beautifully outlined issues of biocompatibility due to shear. Yesterday a paper presented proposed the use of blood flow rates of 600ml/min and as clinicians we do not see obvious problems when using flows of say 400 versus 150ml/min. Could you comment on this apparent tolerance?

LEONARD The issue can be sorted in three parts. Firstly is to take very great care of the blood access and a short 14g needle with a blood flow of 600ml/min is going to really rip up the cells and the major biocompatibility problem will be the strong activation of susceptible cells. It is unlikely to show as haemolysis but more likely as platelet and leucocyte damage. Secondly there are very few substances whose removal is flow limited and there are much better ways of removing more of what is presented to the dialyser than by increasing flow. Finally the other part of the system where we might see trouble under these conditions is at the inlet and outlet to the fibres of the dialysers. When dialysers are made the knife cut must be made across the surface of the potted fibres and it is difficult for manufacturers to control the quality of that cut.

HENNE (Wuppertal) I congratulate you on your excellent survey. There is but one statement which I cannot follow. Many of the facts you mentioned in
respect of biocompatibility were surface related. Why did you exclude then the
decrease of surface area as a means to improve biocompatibility? If you would
reduce the surface of the whole system by a very small amount, holding con-
stantly the performance, in our opinion that would improve the system. In the
last decade hollow fibre devices have been miniaturised from about 1.6m² to
about 0.8m². During this period of time survival rates and morbidity have been
improved as was shown by Kjellstrand from the US statistics. This encourages
us to follow that way furthermore.

LEONARD In the last ten years you have straightened me out on many
occasions and without you I would have made many more mistakes in my
presentation. I agree that if you can reduce the membrane surface area of the
artificial kidney holding performance the same there will be an improvement
in biocompatibility as many of the problems are area related. However, I feel
we have reached the mass transfer limits of the membranes and if we try to
have higher fluxes on the membrane we are going to have more and more rejected
molecules and cells on the surface. As a matter of engineering we are going to
be unable to handle this accumulated material and the result will be protein
denaturation, increased cell membrane interaction, and an inability to permeate
this barrier. I think it will be a long time before we can significantly reduce
surface areas. I think we stand to gain a lot more by increasing areas slightly and
making the conditions on the surface a little more gentle.