Editorial Review

'Dialyser design is the engineers' graveyard'
G E Schreiner over the bar at Stockholm
quoted by D N S Kerr

'Dialyser evaluation is the clinicians' vineyard'
R A Gray over the bars at Dublin and Stockholm

INTRODUCTION

This year's editorial review is controversial. Choice is always so, and the intention is to alert our readers to examine dispassionately a situation which did not exist five, nor ten years ago, since the technology now available was not then in existence. The importance of examining the choice of future therapy is that the real goals of the situation have been lost due to increasing complexities of communication among clinician, physician, bioengineer, patient, immunologist, biochemist, haematologist and surgeon who all contribute to our mutual cause — namely the support of the patient living without renal function.

After discussion with clinicians and bioengineers throughout Europe west and east, there is the distinct impression that we are in no way beginning to deal with the numbers of dialysis candidates originally estimated to be in need of treatment. Do these numbers of people exist? In Scotland alone, figures for terminal kidney disease are 30-35 per million of population. We have, therefore, approximately 150 candidates per annum available for haemodialysis. In the six years since haemodialysis was initiated in Scotland, of 900 original patients, only 60 were receiving regular haemodialysis in July 1971. Among United Kingdom clinicians, there is a feeling that in Britain, at least, tacit approval to stabilise the present extent of the programme, or to curtail it, if suitable argument presents itself, has been given by those responsible for financing the nation's health care.

Policy and clinical reasons for not extending the programme to cope with all candidates are numerous. They include:
1. Occupation of hospital beds by candidates who are suitable for home dialysis, but who are reluctant to leave and thus limit training of new candidates.

2. Reluctance of clinicians, hospital boards and local authorities to initiate home dialysis programmes, despite lip service to such undertakings.

3. Limitation of candidates to those with suitable socio-economic backgrounds and psychological stability.

4. Insistence by clinicians on over-high qualifications of staff who maintain patients and equipment.

5. Disastrous hepatitis outbreaks in hospital renal units among patients, staff and relatives.

If specialists in renal disease fail to refer suitable candidates to haemodialysis units, the results are obvious.

In another sector of our society, the criminal one, we regularly send murderers to prison for 10 to 15 years. In Scotland we have criminals being kept by the State at an annual cost per person of £873.60 and a total annual prison expenditure of £3,534,348. In the UK there are over 40,000 persons in prison who are costing our nation over £30,000,000 per year.

Yet odds are heavily against members of our society being kept alive who have committed no crime whatever, and merely have had the misfortune to contract terminal renal failure. The funds for making the technology available to all who need the assistance of haemodialysis are just not forthcoming.

The priorities of those responsible for the welfare of our citizens are indefensible. The technology exists. Where is the will? Have we a European country with a member of this Association who can quote a higher priority? If so, let him speak. We have no choice.

POLITICAL ASPECTS

As usual, with any technology as complex as one aimed at replacing human kidney function, once a central decision has been made in principle that support is necessary, there is the political choice of method of approach. An attempt will now be made briefly to amplify and suggest some more rational choice for the future than current North American and European approaches which appear to differ markedly in the ways in which they receive Government assistance.

NORTH AMERICAN PRACTICE

In the United States, the individual patient without renal function is basically expected to make his own financial arrangements for running costs of a haemodialysis programme. As a US taxpayer, however, he is supposed to benefit massively from financially assisted programmes of research and development into all aspects of renal disease, technology and devices, coordinated by the US Department of Health, Education and Welfare, National
Institutes of Health and Institute for Arthritic and Metabolic Diseases. A number of private foundations including the John A Hartford foundation also assist financially with specific aspects of haemodialysis technology.

The benefits of such massive approaches are that 'systems-orientated' projects receive coordinated, highly professional management of multiple-aspect programmes aimed at one specific goal — for example a wearable artificial kidney. The drawbacks to such an approach are truly monumental and include:

1. The goal must be correctly defined. Frequently in the past this has not been the case. Should funds be allocated even now towards smaller, more efficient dialysers or to a programme aimed at improving public health hygiene?

2. Systems-orientated research produces goal-orientated projects. These frequently mean spending large amounts of money at several university medical schools or contract research institutes simultaneously, trying to achieve one objective. At best, duplication of effort occurs. At worst, the objective is not achieved within the time limits set for the project by enthusiastic researchers who must bring funds to their particular Medical Centre. If one aspect of the project falls behind schedule, chaos results with the main goals of the system.

3. As well as writing up his research for technical journals, the researcher must turn out great numbers of highly professional, well presented contract reports with a hugh proliferation of paperwork.

4. Should central government funds be increased or restricted due to political contingencies, great pressure may be put for rapid contraction or expansion of research efforts. Such an atmosphere is not conducive to balanced, thoughtful, productive research.

5. There is a notable lack of frank, honest and outspoken criticism by contractors of other contract research programmes. This 'kind' approach minimises possible growth of 'bad images' in contract research and prevents in-fighting among contractors. It also ensures that no one programme receives true appraisal except by the funding agency, which is not always in a position to measure the full benefit, impact (or lack of it) of any one group's work. One is conscious that this subject is highly emotive and will thus not be pursued further here.

6. If a US government contractor aided by NIH funds produces a patentable device or system, present legislation actually inhibits its commercial exploitation. The government controls patents for ideas which it funds and is prohibited by Congress from giving exclusive licenses for any one patent. Thus if a commercial company produces a service based on a
US government patent which is successful, he will probably be faced by a competitor entering into production with a government licence for the same non-exclusive patent. The result is obvious. The Argonne dialyser patent has 20 licensees but is not yet in commercial production.

To sum up, despite a few successes (for example perhaps the Cordis-Dow and Argonne dialysers), contract supported research forces the pace of logical development in materials, designs and systems for dialysis technology either to speed up or slow down productive research. What is often overlooked is that until a certain device is available, progress will not take place by supporting projects with massive injections of government cash. Evolution of dialysis technology has most often occurred without government funds. Examples which have greatly assisted progress in dialysis technology (without central government funding) are Netlon mesh, Heparin anticoagulant, Cuprophan membrane, unplasticised polyvinyl chloride and proportionating pumps.

Governments too have a choice. They have the choice of entering technological fields or organising the locations and personnel to practise the technology. There are many good arguments for voluntarily restricting government activities to the latter and leaving technology to the marketplace.

EUROPEAN PRACTICE

There is fortunately as yet, no coordinated European method of approach to dialysis technology. We appear to have restricted ourselves to dialyser design, purchase of US technology (in the form of imported finished goods or of European located factories of US parent companies). One is conscious that a thread of nationalist pride runs through current research in this field. We have Russian dialysers (Sirotkina, 1971), Swedish dialysers, French ones, German Democratic and Dutch ones, not to mention Norwegian ones old and new. Monitor and dialysate delivery systems are also available in a multiplicity of designs, from Italy, UK, Denmark, Sweden, France, German Democratic Republic and Norway.

Where European governments do give financial assistance to the technology it appears to be done on a much more discriminating basis than the North American approach. There are several reasons for this policy:

1. Spread of the technology is slower than in North America.
2. Where a European government has a Central Social Health Service, it is the main purchaser of devices and services for national health. As such it may wish to participate in developing and defining new areas where equipment is needed.

The problems of a discriminatory research support system include:

1. Individual researchers in Western European countries must spend dis-
proportionate amounts of time seeking funds, and 'putting a good case'. One is immediately reminded of the mythical Dr Grant Swinger who never failed to raise funds for his university in twenty years of proposal writing and lobbying government health departments. Self-justification for the researcher's own effort becomes of paramount importance. Logical discussion of the results of his competitors is the first casualty in the cross-fire which follows in the competition for grant monies.

2. Where one European country develops equipment and attempts to distribute it in several others, frequently not enough effort is spent on providing technical service.

3. There is insufficient open discussion on allocation and distribution of funds by the Health Service Departments of European countries. Clinicians and researchers who wish to pursue clinical programmes are forced to devote unrealistic amounts of time in finding out whether and how to obtain financial support from Health Ministries. This time would be better spent in attending to patient needs, the field originally chosen by the clinician for his career and to which he should be best suited.

For the future, some questions must be answered if a real European artificial organ technology is to emerge:

1. Is it less or more expensive to develop processes and equipment in Europe than to buy the technology from US companies?

2. Would the device designed for dialysis technique in Europe receive full support in the marketplace of other European countries? Let us earnestly hope that the myth that because it was 'made in USA it must be better — I'll try it first' is finally over. It truly deserves to be.

3. Instead of competing, could the researchers of individual countries in Europe concentrate on particular aspects of dialysis technology: Germany for instance on membranes, Sweden on dialysers, Denmark on monitoring units, France on transplantation and Britain on new methods of therapy such as adsorption or diafiltration?

**TECHNICAL EVALUATION AND CONVENTIONAL DIALYSIS**

'Every renal unit has its dialyser mortuary'

Since Kolff and Berk (1944) developed the first clinically acceptable artificial kidney there have been almost 80 different dialyser models produced and an almost equally large number of dialysate delivery systems have come to the market. One important reason for this proliferation is related to the changing accent placed on various aspects of therapy.

At first, the maintenance of life was the prime consideration and as intermittent dialysis became an accepted widespread regime economic considera-
tions in dialyser design grew in importance. Development went through a phase of escalating complexity in monitoring technology to ensure patient safety from technical mishaps, particularly during dialysis.

Anaemia in chronic renal failure and its aggravation by dialyser blood loss has more recently come to the fore as a prime consideration in design and now, in addition, transmission of hepatitis is assuming increasing importance. The relationship of dialysis to uraemic osteodystrophy and neuropathy has received attention but has had little influence on the dialysis regime or dialyser design although a recent suggestion that high efficiency dialysis may aggravate the latter condition might be an indication of future design changes (Christopher et al., 1971; Babb et al., 1971).

It is no longer sufficient, in evaluating dialysers and monitoring equipment, to measure dialysance rates of uraemic products. The literature contains ample data on dialysance by commercial dialysers for urea, creatinine and ion transport rates at varying blood flow rates and there is little point in attempting to achieve a more efficient dialyser which would reduce venous blood concentrations of toxins to zero. Increasing dialysance capacity towards those elusive materials as yet undefined or with unknown molecular weight may have merit, but is hardly a logical basis on which to base further development programmes.

Dialysis therapy has been refined considerably to the extent that it is now regarded by most patients and medical attendants to be little more complex than the regular administration of some drug. Physiological disturbances as a result of excessive ultrafiltration, variable dialysate heating systems and poorly defined phenomena such as backache on commencing therapy or widespread paraesthesiae following heparin administration still occasionally occur and may be recognised readily as such by patients with experience of the procedure.

The circulatory system of the uraemic patient is more sensitive than the normal one to minor variation in circulating volume and even in properly functioning dialysis systems hazardous variations in blood pressure are observed. Patients are occasionally hypotensive after prolonged dialysis without much ultrafiltration having been used.

CONVENTIONAL DIALYSERS, THE CHOICE

Variations in ultrafiltration rate and other technical details of dialysers become apparent on referring to Table I which lists current dialysers, obsolescent models and paediatric devices. Details of suppliers and device type are shown in Table II which lists all machines currently available in the United Kingdom. Details of dialysers available elsewhere in Europe may be obtained by examining the advertisement section of this volume. Currently no official data is available on total and type of dialyser usage in England.
<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Disposable D</th>
<th>Surface area m²</th>
<th>Priming volume</th>
<th>Residual blood loss</th>
<th>Urea transport*</th>
<th>UF rate+</th>
<th>Burst rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraflo 100 (C)</td>
<td>D</td>
<td>1 m²</td>
<td>400 ml</td>
<td>5-10 ml</td>
<td>150 ml/min</td>
<td>500 ml/hr</td>
<td>18%</td>
</tr>
<tr>
<td>(Cuprophan PT 150)</td>
<td>(Cuprophan PT 150)</td>
<td>(Muth, 1969; Easterling et al, 1969; Lowrie et al, 1969)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kii (S) 2 layer</td>
<td>ND</td>
<td>1.02 m²</td>
<td>110 ml</td>
<td>3-11 ml</td>
<td>80 ml/min</td>
<td>300 ml/hr</td>
<td>3%</td>
</tr>
<tr>
<td>(Cuprophan PT 150)</td>
<td>(Kii, 1960; Freeman et al, 1964; Rastogi et al, 1969)</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>AB Gambro (S) 11 layer</td>
<td>D</td>
<td>1.02 m²</td>
<td>130-250 ml</td>
<td>11-30 ml</td>
<td>80 ml/min</td>
<td>250 ml/hr</td>
<td>1%</td>
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<tr>
<td>(Cuprophan 240) 6 layer</td>
<td>(Kii, 1968; Kulatiaka et al, 1969; Muir et al, 1970; Rastogi et al, 1969)</td>
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<tr>
<td>Rhône-Poulenc (S) 10 layer</td>
<td>D</td>
<td>0.96 m²</td>
<td>300 ml</td>
<td>5 ml</td>
<td>95 ml/min</td>
<td>300 ml/hr</td>
<td>0</td>
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<tr>
<td>(Cuprophan PT 150)</td>
<td>(Funck-Brentano et al, 1969; von Hartitzsch et al, 1971)</td>
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<tr>
<td>EX-03 (C)</td>
<td>D</td>
<td>0.84 m²</td>
<td>300 ml</td>
<td>2 ml</td>
<td>130 ml/min</td>
<td>280 ml/hr</td>
<td>2%</td>
</tr>
<tr>
<td>(Cuprophan PT 150)</td>
<td>(Miller et al, 1968; Bergman et al, 1969; Extracorporeal Medical Specialities Inc., 1971)</td>
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Table I (continued)

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Disposable D</th>
<th>Surface area m²</th>
<th>Priming volume</th>
<th>Residual blood loss</th>
<th>Urea transport*</th>
<th>UF rate+</th>
<th>Burst rate</th>
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<tbody>
<tr>
<td>Cordis-Dow</td>
<td>D</td>
<td>1.0 m²</td>
<td>100 ml</td>
<td>-</td>
<td>135 ml/min</td>
<td>200 ml/hr</td>
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<tr>
<td>(Tube Bundle)</td>
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<tr>
<td>(Stewart et al, 1968; Gotch et al, 1969; Keen, 1971; Gotch et al, 1971)</td>
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<tr>
<td>AUE 70</td>
<td>ND</td>
<td>0.6 m²</td>
<td>280 ml</td>
<td>20 ml</td>
<td>85 ml/min</td>
<td>225 ml/hr</td>
<td>-</td>
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<tr>
<td>Twin Minicoil (C)</td>
<td>D</td>
<td>0.9 m²</td>
<td>400 ml</td>
<td>10-15 ml</td>
<td>80 ml/min</td>
<td>100 ml/hr</td>
<td>-</td>
</tr>
<tr>
<td>(Cellophane PT 300)</td>
<td></td>
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<tr>
<td>(Simpson et al, 1967)</td>
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**FORMER MODELS PERIOD 1956-1968**

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Disposable D</th>
<th>Surface area m²</th>
<th>Priming volume</th>
<th>Residual blood loss</th>
<th>Urea transport*</th>
<th>UF rate+</th>
<th>Burst rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin Coil (C)</td>
<td>D</td>
<td>1.9 m²</td>
<td>1,200 ml</td>
<td>-</td>
<td>110 ml/min</td>
<td>200-500 ml/hr</td>
<td>-</td>
</tr>
<tr>
<td>(Cellophane PT 300)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chronacoil (C)</td>
<td>D</td>
<td>0.9 m²</td>
<td>450 ml</td>
<td>-</td>
<td>80 ml/min</td>
<td>120 ml/hr</td>
<td>-</td>
</tr>
<tr>
<td>(Cellophane PT 300)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultraflo 145 (C)</td>
<td>D</td>
<td>1.45 m²</td>
<td>490 ml</td>
<td>5 ml</td>
<td>150 ml/min</td>
<td>500 ml/hr</td>
<td>7%</td>
</tr>
<tr>
<td>(Cellophane PT 300)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kill Original (S) 4 layer</td>
<td>ND</td>
<td>1.8 m²</td>
<td>700 ml</td>
<td>-</td>
<td>165 ml/min (Dialysate flow 5 l/min)</td>
<td>900 ml/hr</td>
<td>-</td>
</tr>
<tr>
<td>(Cellophane)</td>
<td></td>
<td></td>
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</tbody>
</table>

(continued)
### Table I. (continued)

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Disposable D</th>
<th>Surface area m²</th>
<th>Priming volume</th>
<th>Residual blood loss</th>
<th>Urea transport*</th>
<th>UF rate+</th>
<th>Burst rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kil (S) 1 layer</td>
<td>ND</td>
<td>0.51 m²</td>
<td>50-100 ml</td>
<td>-</td>
<td>45 ml/min</td>
<td>125 ml/hr</td>
<td>-</td>
</tr>
<tr>
<td>AB Gambro (S) 6 layer</td>
<td>D</td>
<td>0.55 m²</td>
<td>104 ml</td>
<td>18 ml</td>
<td>65 ml/min</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Meltec (S) (Meltec, 1971; Hoenich et al, 1971)</td>
<td>ND</td>
<td>0.6 m²</td>
<td>80 ml</td>
<td>1 ml</td>
<td>120 ml/min</td>
<td>150 ml/hr</td>
<td>-</td>
</tr>
</tbody>
</table>

*Urea transport: dialysance at blood flow rate 200 ml/min and dialysate flow rate 500 ml/min (Single pass) and recirculation systems up to 6 litres/min.
+Ultrafiltration rate at a transmembrane pressure gradient of 200 mm mercury.

### Table II. United Kingdom dialyser suppliers+

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Type</th>
<th>Supplier</th>
<th>Price (without blood lines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter UF 100</td>
<td>Disposable Coil</td>
<td>Baxter-Travenol, Thetford, Norfolk</td>
<td>£9.00</td>
</tr>
<tr>
<td>Baxter UF 145</td>
<td>Disposable Coil</td>
<td>Baxter-Travenol, Thetford, Norfolk</td>
<td></td>
</tr>
<tr>
<td>Calmic</td>
<td>Disposable Coil</td>
<td>Calmic Engineering, Crewe, Cheshire</td>
<td>Not available</td>
</tr>
<tr>
<td>Nephavan</td>
<td>Disposable Coil</td>
<td>Avon Rubber Co., Medical Division, Birmingham</td>
<td>£5.00</td>
</tr>
<tr>
<td>Twin Mini-coil</td>
<td>Disposable Coil</td>
<td>Avon Rubber Co., Medical Division, Birmingham</td>
<td>£7.50</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Type</th>
<th>Supplier</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>EX-03</td>
<td>Disposable Coil</td>
<td>Extracorporeal Specialities Ltd., Chas. F. Thackray, Ltd., Leeds</td>
<td>£9.00*</td>
</tr>
<tr>
<td>AB Gambro</td>
<td>Disposable Flat-Plate</td>
<td>AB Gambro, Lund, Sweden</td>
<td>£12.00</td>
</tr>
<tr>
<td>Rhône-Poulenc</td>
<td>Disposable Flat-Plate</td>
<td>May &amp; Baker, Ltd., Dagenham, Essex. Medical Plastics Division</td>
<td>£13.50*</td>
</tr>
<tr>
<td>Cordis-Dow</td>
<td>Disposable Tube bundle</td>
<td>Kimal Scientific Products, Ltd., Hillingdon, Middlesex</td>
<td>£9.80</td>
</tr>
<tr>
<td>Kill</td>
<td>Reusable Flat-Plate</td>
<td>Watson-Marlow, Ltd., Falmouth, Cornwall</td>
<td>£285.00</td>
</tr>
<tr>
<td>AUE</td>
<td>Reusable Tubing</td>
<td>T.E.M. Engineering, Gatwick Road, Crawley, Sussex</td>
<td>£300.00</td>
</tr>
<tr>
<td>Grimsrud Dialyser</td>
<td>Reusable Flat-Plate</td>
<td>A/S. Nycotron</td>
<td>Not known</td>
</tr>
<tr>
<td>Meltec Dialyser</td>
<td>Reusable Flat-Plate</td>
<td>Meltec Ltd., Bourne End, Buckinghamshire</td>
<td>£295.00</td>
</tr>
</tbody>
</table>

*The addresses of manufacturers supplying dialysers elsewhere in Europe may be found in the advertisement section of this volume.

*Manufacturer’s policy is to sell this device with blood lines included. No quotation was available without lines.
Defining technical specifications

As mentioned above, variations in technical specifications may produce different patient effects during dialysis, but assuming adequate molecular transport in a dialyser which may vary between machines by as much as 100% (Cestero & Freeman, 1969) the main requirements for dialyser technical specifications are now:

1. Machine disposability to minimise infection transfer.
2. Zero haemoglobin losses (not the < 20 ml figure suggested by Kerr, 1969) to minimise infection transfer risks from transfused blood.
3. Zero loss of essential blood components and clotting factors inside the dialyser.
4. Zero damage to patient blood components and clotting factors while in the extracorporeal circuit.
5. Adequate ultrafiltration rates which imply a surface area of cellulose membrane of not less than 0.6 m² (minimum tolerable rate 250 ml/hr).
6. Minimised physiological and psychological imbalance due to procedure.
7. Lowest possible recurrent cost to patient or community.
8. Device should transport and remove from bloodstream only those components which are responsible for the uraemic syndrome. The explanation for differences in post-dialysis serum toxicity resulting from patient exposure to two different dialysis procedures reported recently by Scribner’s group (Christopher et al, 1971; Babb et al, 1971) are interesting, but not conclusive.
9. Pressure gradient profile in the blood manifold should at all points exceed that of the dialysate pressure profile. In the event of membrane failure, as a safety measure, blood should leak into dialysate and never vice versa.

While it is technically feasible to obtain information on items 3 and 4 above, item 6 remains elusive. Literature reports by clinicians suggest, without data, that a Kiil dialyser is more 'gentle' to the patient than a coil dialyser. This may suggest that a disposable flat plate dialyser will be the chosen conventional device of the future. We have preliminary data from Glasgow Royal Infirmary (Kennedy & Burton, 1971; Lindsay & Muir, 1971) suggesting that some dialysers produce severe damage to platelets, while machines of proper fluid dynamic design such as the Rhône-Poulenc or the Extracorporeal EX-03 minimise or eliminate platelet damage completely (Table III). This phenomenon is directly attributable to machine design since the same pump (Baxter-Travenol Model FUA 14) was used throughout the experiments.

The differences evident in technical performance between different dialyser designs in terms of blood loss and burst rate are in part due to the tech-
Table III. In vivo platelet losses in disposable dialysers

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Type</th>
<th>Platelet loss post-dialysis (10 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambro</td>
<td>Disposable flat-plate</td>
<td>43%</td>
</tr>
<tr>
<td>Rhône-Poulenc</td>
<td>Disposable flat-plate</td>
<td>0% (no statistically significant loss)</td>
</tr>
<tr>
<td>Baxter-Travenol UF 100</td>
<td>Disposable coil</td>
<td>27%</td>
</tr>
<tr>
<td>Extracorporeal EX-03</td>
<td>Disposable coil</td>
<td>0% (no statistically significant loss)</td>
</tr>
</tbody>
</table>

Technical competence of users or investigators. Dialysers which show low blood losses in the hands of some workers, may exhibit higher losses in others due to the use, for instance, of unsuitably low blood flow rates (Will et al, 1970).

Paediatric dialysers

Peritoneal dialysis is the preferred treatment for children with acute renal failure, but intermittent haemodialysis has been shown to be successful for the management of end stage chronic renal failure (Broyer et al, 1970; Shaldon et al, 1969; Fine et al, 1969).

Much is still unknown regarding the effects on growth of long term dialysis and it would seem logical that this therapy should be undertaken in a limited number of centres where facilities for such detailed studies exist. Sandwich dialysers are currently used in paediatric practice, the type of device depending on its priming volume and the patient's body weight. For children less than 30 kg the following plate dialysers are used:

1. Single layer standard Kiil with a priming volume of 175 ml including blood lines
2. Meltec, double layer Kiil with a priming volume of 120 ml including blood lines (membrane surface area 0.6 m²).

Children with body weights in excess of 30 kg can generally be dialysed on adult devices. The Rhône-Poulenc 8 layered device with a priming volume including blood lines of 250 ml, offers a flexible solution to the problem of extracorporeal volume in that layers can be opened or left closed to give varying volumes and membrane areas depending on the child's size.

DIALYSER REUSE

The only possible justification for dialyser reuse is the economic one. Reuse of disposable devices is illogical and against the initial concept of the machine. Arguments against reuse are powerful and many: they include infection transfer risks, increased blood factor losses with successive reuse,
bursts and progressive loss of efficiency in transporting uraemic toxins due to changes in membrane envelope dimensions which increase height of dialyser blood channels.

Future acceptance of dialyser reuse procedures necessitates establishing adequate performance before each successive dialysis. Figure 1 illustrates performance falling with elapsed dialysis time for a number of commercial flat-bed dialysers. Such falls, are in our view, firm contra-indications to dialyser reuse. There are no corresponding curves of urea dialysance versus elapsed dialysis time for coil devices, but a recent clinical trial of the EX-03 machine at Glasgow (Burton, 1971) suggests no loss of performance after 9 hours. Enthusiasm recently shown for repeated machine use, such as recommended by de Palma (de Palma et al, 1969; de Palma et al, 1971) and co-workers should be viewed with extreme caution. There is a noticeable lack of data on dialyser solute clearance with elapsed dialysis time in most of the publications which report machine performances at outset of dialysis.

Fall in dialyser performances, with elapsed dialysis time for different machines, occurs both in vivo and in vitro even on first use and is definitely not recommended for the Argonne dialyser (Markley et al, 1969; Markley & Lavender, 1970). This suggests that a two-fold effect is being observed. The first, increase in blood manifold height due to anisotropic swelling of cellulose membranes, could account for some performance loss. This is being examined by the authors by measuring changes in pressure drop in the blood manifold of dialysers with elapsed dialysis time. In the second effect, low blood velocity (Muir et al, 1971a) and the relative incompatibility of cellophane with blood (Martin et al, 1971) result in the deposition of essential blood factors on the membrane surface so increasing resistance to molecular
transport. Essential blood factors are adsorbed by the membrane surface depending on the chemical composition of the material and increase resistance to transfer of toxins thus impeding membrane performance. A 16% fall in creatinine and 22% fall in urea clearances after one reuse have been observed in the Rhône-Poulenc machine (von Hartitzsch, 1971). Pollard (1987) reported successful reuse of Kiil machines up to 6 times, but extensive blood and fibrin deposits precluded further extensions and such deposits are, in our view, firm contraindications to the procedure.

Figure 2 shows the type of debris deposited from heparinised blood on a

Figure 2. (a) Platelets and red cells deposited on Cuprophan PT 150 membrane from heparinised blood after 4 hours exposure in a dialyser; (b) platelets and red cells deposited on acrylic copolymer dialysis membrane in same experiment as (a) after 4 hours' blood exposure. There are noticeable differences in amounts of deposited cells on the two types of membrane.
cellulose membrane. Despite adequate heparin levels, thrombus initiation is observed and such layers undoubtedly reduce the effective membrane area presented to uraemic blood for mass transfer.

Acceptable dialyser reuse thus depends on the availability of membranes and materials for dialyser blood paths which will not adsorb or damage essential blood factors.

**DIALYSER DAMAGE TO FORMED BLOOD ELEMENTS**

Apart from platelet destruction in dialysers mentioned earlier, virtually nothing is known of the extent, mode or mechanisms of destruction of other formed blood elements flowing in the extracorporeal dialyser circuit. Mechanical deformation of some formed blood elements occurs in blood flowing in capillary tubes, but whether or not permanent damage occurs in these components remains speculative. Such damage might induce biochemical changes which could lead to observed physical deposition and thrombus induction in dialysers, extracorporeal lines and thrombus filters.

Phase separation of red cells and plasma has been observed in tubular flow by many workers (but not previously in rectangular manifolds currently under study by the authors) and changes in vessel and capillary haematocrits predicted (Lih, 1969). Erythrocyte deformation in glass capillaries has been observed (Marple & Hochmuth, 1969) and it is interesting to speculate that red cell deformation and damage in the dialyser circuits might release ADP which could trigger those clotting sequences producing thrombus in some dialyser manifolds.

In vitro flow response by cells in a varying shear situation has been examined while a constant flow rate and velocity profile obtained (Krueger et al, 1969). Damage to cells does not appear significant while laminar flow conditions predominate. Thus more information is required on the effect of the extracorporeal circuit component contribution to blood component damage related effects which lead to thrombus formation.

For the immediate future, to make an unequivocal choice of dialyser for long-term clinical use, clinicians must carry out a task which is impossible for dialyser manufacturers. Clinicians evaluating dialysers should attempt to measure blood component damage at machine inlet and outlet for extracorporeal circuit components, including dialyser and blood pumps. Typical blood factors which require investigation for potential damage include:

1. Platelets
2. Leucocytes
3. Reticulocytes
4. Polychromatophilic erythroblasts
5. Haematocrit
6. Total haemoglobin
7. Free haemoglobin
8. Haptoglobin
9. Methaemalbumin
10. Fibrinogen
11. Fibrin degradation products
12. Euglobulin lysis time
13. Activated partial thromboplastin time

The main formed blood elements red cells, platelets and plasma proteins undergo various degrees of trauma while flowing through the extracorporeal circuit due to the effects of both blood pumps and dialysers themselves (Gral et al, 1969a, b; Hyde & Sadler, 1969; Kusserow et al, 1969; Papadimitriou et al, 1969; Kaplow & Goffinet, 1968). Causes of damage include the following factors:

(a) Mechanical shear and emboli caused by the pump as clinicians resort to mechanical means to circulate blood through the extracorporeal circuit rather than use the patient's heart (Ward et al, 1971). Use of mechanical blood pumps is accelerating with the demise of the Scribner-Quinton shunt and the increasing popularity with clinicians and patients of the Cimino-Brescia fistula.

(b) Inadequate haemodynamic design of the blood manifolds, inlet and outlet ports in the dialyser.

(c) Phase separation of plasma and red cells due to unsuitable blood velocity profiles with flow down the dialyser manifold.

(d) Device fabrication in materials and types of plastic which are unsuited to medical use.

DIALYSER SELECTION

Clinicians are now presented with a bewildering array of monitoring and dialyser designs which should all perform the same function. But do they? At least there is some choice now, while five years ago the clinician beginning conventional dialysis in a European country could rely only on imported Kilian machines or disposable coils.

Disposable dialysers

Manufacturers of disposable dialyser equipment can go no further than they have done up to the present by bringing more devices to the market place. They must find a method, if the clinician will not do so, of ensuring frank and open methods of stating the advantages and disadvantages of particular designs even if short-term economic losses follow. The mature clinician and bioengineer has more respect and will assist the manufacturer of each
Figure 3. Flat-plate machines: Gambro and Rhône-Poulenc dialysers

Figure 4. Hand assembly of a Watson-Marlow Kil with Cuprophan PT 150 membranes
machine who aims to improve his basic design. He will have none for the
producer who shops around various clinical centres in a search for the most
favourable evaluation.

At present if a haemodialysis centre contemplates a particular choice of
disposable design, the clinician may choose a disposable flat-plate design
such as the commercially available Rhône-Poulenc or Gambro dialysers
(Figure 3). One is immediately impressed by the ease with which either
machine is put into use with a minimum of preparation time, unlike the
craftsman-like assembly of a standard Kil (Figure 4).

With coil machines there are immediately obvious differences (Figure 5).

Figure 5. Coil dialysers: Nephravan (top left), Baxter-Travenol UF 100 (top right),
Calmic (left) and EX-03 (right).

Although we predict that the most efficient coil devices will ultimately prove
to cause greater blood trauma than the best flat-plate machine, coil dialysers
are generally more technically efficient in clearing blood poisons than flat-
plate machines (Figure 6) due to higher blood velocity profiles, better mixing
of both dialysate and blood and low blood channel heights of optimised dimen-
sions. The Extracorporeal EX-03 dialyser has immediate advantages over
other coil designs in terms of storage bulk, lower membrane surface to
which essential blood components may adhere, and obviously simpler coupl-
ings in that there is only one blood inlet and one outlet to the device as well
as high dialysance efficiency. In addition, this particular design does not show a significant drop in urea clearance with elapsed dialysis times up to 10 hours (Kennedy & Burton, 1971) unlike some flat-plate designs (Figure 1).

Current coil designs can produce high and, at times, excessive ultrafiltration rates and would benefit from the construction of more rigid plastic housings which could be subjected to controlled dialysate pressures and, therefore, ultrafiltration rates. The other present restriction inherent in high blood path resistance devices is the mechanical blood pump requirement with its resultant damage to cellular elements and the use of further control systems.

Another disposable device using cellulose membranes in tubular form is the Cordis-Dow dialyser shown in Figure 7. This unusually compact system stores approximately one square metre of membrane area in a size approximately 8” x 3” (20.3 x 7.6 cm).
Non-disposable dialysers

Despite efforts to produce high efficiency flat-plate machines using less than one square metre surface area (Babb, 1967; Muir et al, 1969; Meltec, 1971; S/S. Nycotron, 1970) ultrafiltration rates have, to some extent, restricted clinical use of such devices with cellophane based membranes. With the development of novel membrane systems (Muir et al, 1970a) having improved water transport properties, the introduction of small plate devices as illustrated in Figures 8 and 9 will be practical. Finally, another reusable device, the AUE 70 (membrane area 0.6 m²) dialyser made in the German Democratic Republic, using cellulose tubing in a continuous length, is shown in Figure 10.

After choosing a dialyser system and operating it for a period of months, the clinician presently has no technical data to compare any one of the above designs with another in the following areas:

1. Rate of loss of patient haematocrit, leading to blood transfusion requirements.
2. Platelet loss during dialysis terminating in a blood hypocoagulable state.
3. Comparative formed blood factor (cellular and protein) damage during haemodialysis.
4. Dialysis clearance with elapsed dialysis time. Considerable quantities of formed blood elements are presently lost to the patient in routine maintenance haemodialysis by discarding the dialyser at termination of dialysis. This of course does not mean that reuse should be contemplated since plasma proteins and fibrin are deposited on all internal blood paths of dialysers continually.
Figure 8. The (0.56 metre\(^2\) membrane area) Ross-Muir dialyser

Figure 9. The Ross-Muir dialyser in clinical use
Dialyser sources

Present suppliers of dialysers in the United Kingdom are listed in Table II.

Monitor units

Dialysate supply and patient monitors are outside the scope of this article. Advice should be obtained from respective dialyser suppliers for appropriate supply units. Present United Kingdom manufacturers of monitor units include Baxter-Travenol, Lucas, Dylade, Watson-Marlow and Cambridge Instruments. This list is not exhaustive.

CONCLUSION

The treatment of chronic renal disease by haemodialysis is a technically feasible means of prolonging life and rehabilitating chronically ill individuals, but could be available for many more than are currently receiving therapy. This might be achieved by:

1. A reduction in the proliferation and scattered usage of multiple dialyser and dialysate delivery system designs within the National Health Service. Unlike drug therapy or surgical procedures the function of the hardware depends very little on the personal touch of the operator and, in fact, can be standardised.

2. A definition (reviewed from time to time) of the current needs and optimum specifications for dialysis therapy in uraemia by a national body of specialists.
3. A national evaluation centre for haemodialysis equipment, membranes and dialysis procedures.

4. A national decision on priority areas to receive future financial support in research topics selected from renal transplantation, preventive screening, diafiltration, adsorption or conventional haemodialysis.

IATROGENIC FACTORS OF MACHINE AND SYSTEM

Possibly the most important part of dialysis patient care is that of minimising trauma. The task of establishing dialysis centres is now over and the present primary objective should be to improve quality of patient care and quality of life for patients on machines, and thus survival rates will increase and improve.

It is possible that in poorly maintained patients we may be seeing a little of the 'artificial heart syndrome'.

In a hypothetical example, a patient on certain dialysers experiences massive blood trauma during weekly spells on the machine. His system is thus hypercoagulable at initiation of dialysis. After losing blood and receiving gross damage to all his circulated blood for 12 hours, his system becomes hypocoagulable. Between dialysis, his circulatory system, bone marrow and liver must work doubly hard to restore the status quo of haematological factors and he has no system to excrete waste products of the process, except his next dialysis. The long-term results are obvious and predictable.

This state has been described by Kolff (Lyman et al, 1971; Kwan-Gett et al, 1971) in his group’s attempts to implant prototype artificial heart designs in sheep and calves. It should be obvious that any such damage to formed blood elements in a prototype should produce utmost pessimism about the inherent design. Once more, by concentrating on blood output and efficiency, we have concentrated on single function wrongly, of an artificial organ without considering the long-term biological effect. The same is true of dialyser design. We have spent most of our efforts in trying to miniaturise and increase machine efficiency without full consideration or knowledge of methods of measuring physiological trauma, blood damage and secondary organ damage or overloading.

Much effort must therefore be expended in future extracorporeal circuit design to be aware of the problems inherent in systems and to minimise iatrogenic effects of:

1. Blood pumps which produce high shear in blood or pump air.

2. Extracorporeal blood lines whose surfaces adsorb essential blood components and initiate surface-induced thrombus despite anticoagulant therapy.

3. Changes in cross-sectional dimensions of extracorporeal circuits
presented to flowing blood which cause solution or dissolution of air and dissolved blood gases.

4. Dialysers or therapeutic systems which irreversibly alter blood factors.

THE CHOICE OF NEW TECHNOLOGY

Which direction should we take for the future? The choice lies among:

(a) Conventional dialysis
(b) Unconventional dialysis
(c) Renal transplantation
(d) Preventive patient screening and educational preventive propaganda
(e) Abandonment of present techniques.

Shall we design smaller dialysers? American workers having spent the past seven years in attempts to make machines of 0.5 m² surface area with performances equal to that of the Kii machine with 1 m² membrane area are now attempting to build larger designs up to 2.5 m² in area to improve dialysis rates of 'middle-range' molecular weight components.

CONVENTIONAL DIALYSIS

As mentioned earlier there is a definite trend in conventional dialysis to smaller, more efficient dialysers which also minimise damage to formed blood elements and blood loss. On the monitoring side, a welcome trend to simpler, safer dialysate delivery systems is evident. Patient monitoring of blood biochemical components is being minimised once relative stability of metabolism is achieved. Patients are also much in favour of the arteriovenous fistula, rather than the 'permanent' in-dwelling plastic shunt.

On the technical side, attempts have been made to find alternatives to that well-tried old and reliable Cuprophan membrane with varying degrees of success (Muir et al, 1970a; Muir et al, 1971b,c). New acrylic vinyl copolymer membranes are under test. Biological testing is reported elsewhere in this volume (Muir et al, 1971d) and human clinical evaluation is underway in the absence of adverse reactions from dog studies (Martin et al, 1970).

During the last year the Journal of Medical and Biological Engineering has contained so many mathematical models for haemodialyser performance that the reader is referred to Journal communications too numerous to detail here, with the exception of one by the author! (Gaylor et al, 1970). Mathematical modelling of dialysier performance is of limited interest to the clinician but highly relevant to the bioengineer in attempts to improve dialysier efficiency. Attempts have been made with limited success to produce disposable blood envelopes and dialyser packs (Flower, 1970; Detrice, 1967). Disposability of such packs eliminates sterilisation requirements immediately prior to dialysis as packs can be supplied pre-sterilised.
Resistance to blood toxin removal through the semipermeable membrane can be reduced on the dialysate side of the membrane by increasing turbulence of the washing fluid. This may be achieved by introducing air or carbon dioxide into dialysate in order to increase turbulence (Kolobow et al., 1964). Another school of thought (Ab Sievert, 1970) suggests that deaeration of dialysate in order to remove a stagnant layer on the dialysate side of the membrane due to tiny bubbles will increase toxin removal rates. This deairing of dialysate is carried out under reduced pressure in a compartment outside the dialyser.

Improved dialysance rates have been reported (Ross & Muir, 1971) as a result of machine design improvements.

Several workers (Sirotkina et al., 1971; Babb et al., 1964; Shinaberger et al., 1966; Longmore, 1963) have improved the utilisation of membrane area by modifying membrane support and dialysate flow geometry on the rinsing fluid side of the membrane. A membrane support system using jet streams of dialysate has been reported (Boissevan, 1970). A natural development of the flat plate design dialyser was that of a stack plate dialyser (Esmond, 1966). Parallel flow dialysers having similar total surface area to that of the Kiil can be supplied as compact pre-sterilised and disposable machines (Ab Gambro, 1967; Alwall, 1968; Rhône-Poulenc, 1971).

Coil Dialysers

The original coil haemodialyser (Kolff et al., 1956) has undergone several modifications in blood and dialysate flow geometry, although the basic design has remained unchanged in principle. Dialysers have been reported in which blood flows across cellulose membranes containing flowing dialysate (Dow Corning, 1967; Kolobow et al., 1964; Capon Heaton, 1965).

The disadvantages of coil dialysers, namely the necessity for blood pumping and high blood loss in the dialyser have been minimised in recent years due to improved manufacturing technology (Baxter Laboratories Inc., 1966; Clark et al., 1968).

Other types of dialysers

A haemodialyser utilising long flat cellulose tubing mounted by means of perspex guide members which provide a serpentine channel for liquid flow — blood passing inside the tube and rinsing fluid outside (Fechner et al., 1967; Willgerodt, 1971) — is in clinical use.

A tidal flow dialyser (Bluemle, 1965) consisting of a disposable pleated strip of membrane sheet without membrane support has been reported.

UNCONVENTIONAL DIALYSIS

While there appears to be little to recommend passing uraemic blood over
non-specific adsorbents which remove essential blood components such as
cations, platelets and fibrinogen as well as toxic poisons, alternatives to
conventional dialysis do exist, at presently unknown cost.

**Adsorption and Chemisorption** may be coupled with dialysis where improve-
ments in adsorbent materials other than charcoal make possible the removal
of poison components from dialysate streams after transfer through semi-
permeable membranes from the patient’s bloodstream. Some investigations
have been made into identifying toxins which should be removed (Dunea &
Kolff, 1965).

**Microcapsules** may be used for direct exposure of uraemic blood to encapsu-
lated adsorbents, biodegradation or enzymatic conversion of toxins and urae-
mic poisons by encapsulated enzymes to more readily expelled materials in
the intestine (Gardner et al, 1971).

**Diafiltration** Plasma is separated from red cells, dialysed then reconstituted.
This process most nearly corresponds to the mode of operation of the human
kidney.

Unfortunately, while most effort is presently being focused on biochemi-
cal removal of uraemic toxins, there is insufficient emphasis being given to
the physical effects and problems of damage to formed blood elements by the
use of the above three processes.

Further, severe osmotic imbalance could be caused to blood and plasma
flowing through membrane envelopes surrounded on the outer walls by poly-
meric gels which produce very large pressure effects in aqueous solutions.

Some of these effects are obviously now evident to workers in this field,
who are taking a much more cautious approach after the initial enthusiastic
reports on diafiltration that appeared about three years ago.

Points to be remembered by optimistic researchers in unconventional
dialysis are:

1. The compounds responsible for the uraemic syndrome are not fully
identified. Apart from the simplest components, no one yet knows the
molecular identity of compounds to be adsorbed. How then do we
design adsorbents?

2. A balance between ion and metabolic waste product removal must be
obtained.

3. A separate membrane device may be required to provide necessary
ultrafiltration.

4. Blood flow and percolation through adsorptive devices means adsorption
of essential blood factors as well as toxic materials. Percolation also
means channelling and inefficient flow. Adsorbents should therefore
be presented to the blood in flat sheet form for laminar flow with a
permeable membrane interposed between blood and adsorbent which does not retain essential blood components after exposure.

5. Adsorbents should be non-volatile and incapable of contaminating blood either by diffusion across membrane barriers or by secondary chemical reactions inherent in the process.

6. No unintentional enzymatic reactions should occur with blood components or stomach mucosa by orally ingested microencapsulated systems during the digestive process.

Adsorption and microencapsulation techniques

The possibility of removing blood constituents and, in particular, blood toxins by adsorption is long established (Bock, 1920). This has led many workers to consider the use of adsorbents in the treatment of renal disease, either as an alternative to haemodialysis by adsorbing toxins direct from the bloodstream or as a means of improving haemodialysis by adsorbing toxins from the dialysate to permit dialysate recirculation. The adverse effects caused by the direct contact of blood with adsorbents has resulted in the introduction of coated adsorbents and the application of microencapsulation.

Direct blood perfusion: removal of constituents from blood

(a) Charcoal Attempts to remove uraemic waste metabolites and blood toxins by adsorption with activated charcoal have been widespread (Yatzidis, 1964, 1965, 1966; Dunea & Kolff, 1965; Blaney et al, 1966, 1968; Hagstam et al, 1966; Jutzler et al, 1966; Kolobow & Dedrick, 1968a, b; Sparks et al, 1966; Twiss & Paulssen, 1966; Dedrick et al, 1967; de Myttenaere et al, 1967; Barakat & MacPhee, 1970). Although charcoal is unable to remove urea, bilirubin or water, it is able to remove creatinine, uric acid, barbiturates, salicylates and glutethimide (Decker et al, 1968; van Leer et al, 1969). It has been claimed (Yatzidis, 1964; Dunea & Kolff, 1965) that the treatment of patients with chronic renal failure by this method can result in a clinical and biochemical improvement. However, methods involving the direct contact of blood with activated carbon are unsatisfactory. With even short perfusion times, the blood platelet count is reduced by at least 50% and there is a reduction in the white blood cell level (Andrade et al, 1971a, b). Carbon particles may also enter the circulation and lodge in the kidneys, liver, spleen and lungs (Hagstam et al, 1966). Where charcoal columns are used, efficiency is reduced by caking and there is the possibility of red blood cell loss.

(b) Ion-exchange resins The treatment of renal disease by blood perfusion over ion-exchange resins has been considered by several groups of workers (Muirhead & Reid, 1948; Kessler et al, 1953; Bronniman, 1955; Zinsser & Cohen, 1955; Schechter et al, 1958a, b; McLaughlin et al, 1959, 1960; Moore

(c) Coated adsorbents To eliminate some of the problems caused by direct contact of blood with activated charcoal, the use of carbon coated with poly (hydroxyethyl) methacrylate has been suggested (Andrade et al, 1971a, b). This is claimed to reduce platelet loss and caking of the adsorbent. No evidence has been given regarding the possible reduction in white blood cell count and coating reduces the rate of removal by about 20%.

(d) Microcapsules As an alternative to direct haemoperfusion, the microencapsulation of adsorbents has been proposed (Chang, 1966; Chang et al, 1966, 1967; Levine & La Course, 1967; Chang et al, 1968; Chang & Poznansky, 1968a, b; Suzuki et al, 1968; Chang, 1969a, b; Chang & Malave, 1970; Chang & Loa, 1970; Chang, 1971; Chang et al, 1971; Sparks et al, 1969, 1971; Shigeri & Kondo, 1969; Gardner et al, 1971).

Semipermeable microcapsules were originally proposed as a means of reproducing some of the properties of biological cells (Chang, 1964). An enzyme is enclosed by a membrane which prevents passage of the enzyme but allows the passage of substances to be acted on by the enzyme. The idea was later put forward (Chang, 1966) that a compact artificial kidney could be formed by packing semipermeable microcapsules into an extracorporeal shunt through which blood perfuses continuously. Clinical evaluation of albumin-coated cellulose nitrate microcapsules has been reported (Chang & Malave, 1970; Chang et al, 1971). The adsorbent used was activated charcoal which is unsatisfactory for the removal of urea, sodium, potassium, phosphate or water. It has been suggested (Sparks et al, 1969, 1971) that urea could be removed by ethylcellulose microcapsules containing oxidised starch or a combination of urease and ion-exchange resin. Since a single adsorbent cannot meet the requirements, work has been done on a multicomponent microcapsule system containing urease, ammonia chemical binder, activated charcoal binder and ion-exchange resin binder (Gardner et al, 1971). Cellulose acetate butyrate microcapsules, suitable for oral ingestion, are proposed.

(e) Removal of constituents from dialysate Adsorbents have been used for the removal of waste products from dialysate with a view to achieving regeneration of dialysate and a reduction in dialysate volume (Gordon et al, 1968, 1969, 1970, 1971; Better et al, 1970). The method requires the use of urease, zirconium phosphate, zirconium oxide and activated carbon. Urease
converts the urea to ammonia which is adsorbed by the zirconium phosphate. Phosphate is removed by the zirconium oxide and creatinine and uric acid by the activated carbon. Removal of substances from the dialysate poses less problems than removal from the blood but it is obvious that a combination of adsorbents is necessary and that efficiency will be reduced at high dialysate flow rates. However, the view has been expressed (Scribner, Transactions. American Society for Artificial Internal Organs, 1971, page 258) that the system described above is now ready for use in home haemodialysis.

Diafiltration

Diafiltration as an alternative to dialysis for extracorporeal purification of blood was first mentioned by Henderson et al (1967). Diafiltration was defined as the process of subjecting plasma or blood to ultrafiltration and simultaneous reconstitution with a balanced saline solution. Ultrafiltration has been defined as the hydraulic pressure activated separation of solutions into their individual components by passage through semipermeable membranes (Michaels, 1968).

Diafiltration is an engineer’s attempt to mimic the action of the human kidney. 'The first step in urine formation is production of an ultrafiltrate of plasma by glomerular filtration. Large molecules such as plasma proteins and lipids are sieved out, but small molecular weight solutes are passed'. (Abbrecht, 1968). This corresponds to the ultrafiltration step of diafiltration. In the tubules of the kidney, water and freely filterable plasma constituents such as glucose and sodium are reabsorbed. This corresponds to the reconstitution step of diafiltration. Thus diafiltration is closer to natural kidney function than dialysis.

The following advantages are expected from diafiltration compared to dialysis (Bixler et al, 1968a, b):

1. Clearance of higher molecular weight toxins
2. Removal of all relatively low molecular weight toxins without molecular weight selectivity
3. Improved ultrafiltration of water to relieve oedema.

Process

Bixler et al (1968a) also discuss three possible geometries for diafiltration:

1. **Sequential diafiltration**  The reconstituting fluid is mixed with the blood ahead of ultrafiltration
2. **Simultaneous diafiltration**  The reconstituting fluid is mixed with the blood during ultrafiltration
3. **Staged sequential diafiltration**  The ultrafilter is divided into stages and the blood is diluted with the reconstituting fluid before each stage.

Bixler and his colleagues theoretically evaluated the three geometries with
respect to membrane area, volume of reconstituting fluid required, ease of fabrication, ease of operation, and capital cost. They recommended sequential diafiltration. A schematic diagram of sequential diafiltration is shown in Figure 11.

Bixler et al (1968a, b) have done a theoretical process design for an artificial kidney utilising sequential diafiltration. They estimate that for a treatment time of 8 hours and blood flow rate of 300 ml/min, a diafilter membrane of 0.47 m² and 67 litres of reconstituting fluid will be required. The priming volume would be 100-200 ml.

Dorson and Markovitz (1968) and Brown and Kramer (1968) propose diafiltration systems with an additional stage, a hyperfilter. This system is diagrammed in Figure 12. It is hoped that this extra stage will lead to a wearable artificial kidney. The function of the hyperfilter is to separate the water from the solutes in the ultrafiltrate. This reduces the requirements for reconstituting fluid and permits the design of a wearable artificial kidney. Brown and Kramer have designed a kidney on this basis. It weighs 5 pounds, and requires approximately 3 watts of power. The patient would have to ingest 25 g/day of glucose and 5 l/day of water. The concentrated electrolyte

Figure 11. Sequential diafiltration

Figure 12. Wearable artificial kidney
make-up solution will be approximately 350 g/day, and the patient will require two daily loadings.

The advantages of this system are convenience and lack of fluctuations of blood toxin concentrations as occurs with dialysis.

Kinetics and design

The kinetics of ultrafiltration are complex. An introduction to the kinetics can be found in Michaels' (1968) article 'New separation technique for the CPI', which is an excellent introduction to ultrafiltration. Lightfoot (1968) and Macey and Wolf (1960) have done formal analyses of ultrafiltration kinetics. A model which shows the effect of normal serum proteins on Donnan ion equilibrium has been developed by Terepka et al (1970).

Ultrafiltration kinetics are concerned with the term 'membrane rejection efficiency'. The membrane rejection efficiency is defined as the fraction of solute present in the blood which is retained by the membrane. The membrane rejection efficiency for membranes proposed for diafiltration is independent of applied pressure, but only depends on the molecular size and charge of the solute. The rejection efficiency increases with molecular weight and charge. The ultrafiltration rate is independent of the applied pressure and membrane permeability, except at very low pressures or for low permeability membranes. The ultrafiltration rate is proportional to the logarithm of the solute concentration.

The design of an ultrafiltration system centres around the design of a satisfactory ultrafilter. The main design hurdle is protein polarisation. Bixler et al (1968a, b) have done most of the work appearing in the literature with respect to design of devices. They concluded that blood channels approaching capillary dimensions would be attractive. Satisfactory performance could be achieved with 5-10 mil (0.005-0.010 in., 0.013-0.025 cm) channels requiring about 1 m² of membrane and needing a blood pump.

Membranes

The heart of the diafiltration system is the semipermeable membrane. Michaels (1968) presented a table of anisotropic ultrafiltration membranes available in 1968. These membranes consist of a surface layer 4-200 x 10⁻⁶ in. thick of fine pore texture polymer supported by a much thicker, 2-5 mil (0.002-0.005 in., 0.005-0.013 cm) layer of open celled, microporous sponge. These membranes have high hydraulic permeability, high strength, and the ability to block the passage of small solute molecules. Reflection coefficient data are presented by Henderson et al (1967). They show data for a membrane with 0 reflection coefficient for solutes of molecular weight of 210. The reflection coefficient linearly increases to 1 for molecular weight of 800. Thus urea, glucose, and electrolytes would be completely passed, but inulin and proteins would be retained by the membrane.
Film cast membranes are available made of cellulose acetate (General Atomics, Aerojet-General, Havens Ind., Am. Stand.), cellulosic esters (Millipore Corp. P), polyelectrolyte complexes, olefin substitutes, aromatic polymer (Amicon Corp., Dorr-Oliver), and cellulosic materials (Abcor Corp., Millipore Corp.). The polyelectrolyte complexes are made of the precipitated polyelectrolytes, sodium polystyrene sulphonate and polyvinylbenztrimethyl ammonium chloride in stochiometric proportions. Felt backing membrane support was used (Henderson, 1967). Shinaberger et al (1969) used cellulose acetate membranes made of 10 parts cellulose acetate, 30 parts acetone, 5 parts water and 6 parts tartaric acid.

Some of these membranes have been used by experimenters. Henderson et al (1967) and Bixler et al (1968a, b) have tested the Amicon Corp. polyelectrolyte complex membranes. They achieved water flux rates greater than $3.25 \times 10^{-2}$ ml/min/cm$^2$. at 10 p.s.i. Shinaberger et al (1969) tested Aerojet-General Corporation’s cellulose acetate membranes. Dorson and Markowitz (1968) tested Universal Water Corporation’s cellulose acetate membranes. Brown and Kramer (1968) investigated the performance of Abcor Corporation’s cellulosic membranes.

It is impossible to compare the performance of these various membranes on the basis of the insufficient data in the literature. An evaluation of a membrane would have to consider the following factors:

1. Reflection coefficient for toxins and electrolytes
2. Reflection coefficient for proteins
3. Strength
4. Pressure gradient required
5. Ultrafiltration rate
6. Pyrogenicity and thrombogenicity.

The effects of the Diaflo$^R$ membranes of Amicon Corp. on proteins have been investigated by Blatt et al (1965) and Pollak (1968). Diaflo ultrafiltration appeared to have no effect on proteins when the proteins were examined by electrophoretic, immuno-electrophoretic, and quantitative immunodiffusion methods. Neither Diaflo$^R$ membranes (Brown & Kramer, 1968) nor Aerojet-General Corporation’s membranes (Shinaberger et al, 1969) are pyrogenic. Abcor Inc. membranes and Diaflo$^R$ membranes are non thrombogenic (Brown & Kramer, 1968).

Protein polarisation

Protein polarisation is the accumulation of proteins at the ultrafiltration membrane interface. The phenomenon occurs when treating solutions containing proteins (Henderson et al, 1967; Michaels, 1968; Bixler et al, 1968a, b; Brown & Kramer, 1968). For example when plasma was used instead of water
in an ultrafiltrate cell at 15 p.s.i. with Diaflo\textsuperscript{R} membranes, ultrafiltrate formation fell by 60-70\%, from $6 \times 10^{-2} \text{ ml/min/cm}^2$ to $2.0 \times 10^{-2} \text{ ml/min/cm}^2$ (Henderson et al, 1967).

Many writers propose a theory to explain protein polarisation. It is generally agreed that protein polarisation is due to the fact that proteins are carried to membranes by convection at a faster rate than removed by molecular or eddy diffusion (Abbrecht, 1968; Bixler et al, 1968a, b; Brown & Kramer, 1968). Thus it would be expected that polarisation would tend to occur for a solute which (1) is slow diffusing; (2) for which the membrane is impermeable; (3) is relatively more concentrated in the solution, and (4) under non-turbulent conditions. Also, the polarisation layer would increase along the length of a channel until the diffusion and convection fluxes were equal.

The solution to the protein polarisation problem will have to be found in the design of the ultrafiltration device. 'Concentration polarisation of proteins appears to be solvable by proper control of the fluid geometry of the system'. (Bixler et al, 1968). Changes in the membranes would prove to be futile, since protein polarisation is not due to membrane properties but rather results from the ultrafiltration process.

Michaels (1968) claims that it is prohibitively costly because of energy requirements and pumping equipment to use turbulent flow to control polarisation. Also, haemolysis would be a problem with turbulent flow. He claims that laminar flow through thin, 5-10 mil. (0.005-0.010 in., 0.013-0.025 cm) and short, 1-4 in. membrane channels would be the best method of ultrafiltration. Bixler et al (1968) analyse various possible designs for the ultrafilter. They suggest a clinical diafilter with 5 to 10 mil. channels and channel length of 20-100 cm. The flow would be laminar. With channels of this size, the red blood cells may scrub away some of the polarisation layer.

Clinical trials

Only Shinaberger et al (1969) report clinical tests. They used cellulose acetate membranes from Aerojet-General Corporation in a Mini-Klung dialyser. The test was unsuccessful. They had problems with protein polarisation; clotting because of the high viscosity of the ultrafiltrate; and low dialysance due to the thick backing membrane they used.

They also tested two Kil dialysers in series, the first with Cuprophan\textsuperscript{R} and the second with the cellulose acetate membrane. A 68 kg male lost 2.5 kg in 130 minutes.

Their tests indicate that there is a need for a specially designed dialfiltration membrane.

Future of diafiltration

Diafiltration shows great promise for two applications:
1. The rapid control of oedema
2. The wearable, continuous artificial kidney.

The superiority of dialfiltration compared to dialysis for control of oedema has been demonstrated by Shinaberger et al (1969). Brown and Kramer (1968) are considering a prototype of a wearable haemodialfiltration kidney.

Dialfiltration should not yet be considered as a replacement for conventional dialysis, as the 24 hour weekly treatment currently available. No advantage can be foreseen for dialfiltration. It is questionable whether the speedier treatment which may be available with dialfiltration could be tolerated by the patient. Also, dialfiltration has the disadvantage that the reconstituting fluid would have to be sterile and non-pyrogenic.

The main impetus of future work should be towards the development of a device to use existing membranes. Until a device is available which controls or minimises protein polarisation, it is impossible to be sure of the place of dialfiltration in control of kidney failure. Some protein polarisation in the form of depositing specific plasma globulins which inhibit thrombus initiation on some membrane surfaces is beneficial, but non-specific surface deposition of proteinaceous materials is presently the main contraindication to the application of dialfiltration with cellulose acetate membranes.

The development of new membranes should be done with regard to the criteria discussed in the section on 'Membranes'. However, without a clinical device, the evaluation and comparison of different membranes and the development of new membranes will be difficult.

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