Today's Treatment

Diseases of the urinary system

Prospects for the treatment of renal diseases

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Therapeutic advances in treating renal disease have demanded considerable medical resources during the past decade. Most of these resources, both manpower and financial, have been required for the dialysis and transplantation of patients with end-stage renal disease. Prospects of extending these treatments to all who may profit from them depend on the availability of sufficient health resources and on the medical priority accorded to extending the lives of patients who would otherwise die in renal failure. Prospects of reducing the numbers of patients with end-stage renal disease hinge on research into the primary renal diseases from which they suffer and into treatments to prevent these diseases progressing.

Reducing progressive renal disease

The causes of end-stage renal failure in patients needing dialysis and transplantation are listed in the table. These are the diseases that must be prevented or whose progression must be averted.

Glomerulonephritis appears to be the most important, but this has been confirmed by biopsy in relatively few cases. Among those biopsied, in 32.5% of the European and 28.7% of the British cases the histological diagnosis was "advanced sclerosing glomerulonephritis," which implies that almost one-third of patients had presented for diagnosis at a stage of the

illness when there was little opportunity for therapeutic impact. Important antecedent events are often missing from the histories of these patients, but serial biopsies in groups of patients make it clear that an apparently innocuous attack of acute nephritis even decades before patients experience any of the symptoms of renal failure may result in progressive chronic glomerulonephritis, even in the absence of persisting proteinuria. It is not at all clear how much of this slowly progressive disease is due to continuing immunological factors, how much is caused by intermediate inflammatory and sclerosing factors, and how much depends on vascular and ischaemic damage developing. Long-term studies will be necessary to disentangle these factors and to assess any attempt at treatment. Furthermore, the problem of how to detect early progressive disease in asymptomatic patients ensures that it will be difficult to reduce this large number of patients needing renal replacement treatment.

Morphological classifications by no means clarify the relative importance of immunological, ischaemic, infective, or inherited factors in determining the obliteration of nephrons. The classification given in the table implies a greater diagnostic confidence than most critical physicians enjoy. A further example of confusing nosology is the high proportion of cases recorded as chronic pyelonephritis. Progressive renal disease could probably not have been arrested in any appreciable number of these patients by eliminating bacterial infection alone. Nevertheless, there may prove to be a sub-group of these patients with interstitial nephritis whose disease could be due to toxic substances, which future knowledge may enable us to eliminate from the environment.

A notable advance has been the delineation of the nephropathy due to analgesics. The removal of phenacetin from combined analgesic preparations may prove to have been only one example of how progressive renal disease can be prevented. The kidney is uniquely able to concentrate chemicals, drugs, and metabolites, which make it especially vulnerable to these insults. Evidence to implicate such substances, however, is hard to come by and depends on shrewd observation.

CONTROL OF BLOOD PRESSURE

Drugs for effective and acceptable lowering of blood pressure have reduced the proportion of patients with hypertension who die in renal failure. In the future, better control of blood pressure and the wider and earlier application of continually improving drug treatment is sure to extend this benefit. Where hypertension is secondary to some other primary renal disease, good control blunts this potent factor for the acceleration of progressive disease. Early detection of hypertension and thorough application of drugs for its control by general physicians and cardiologists offer a prospect of reducing the number of patients who would otherwise gradually develop progressive arteriolar

*Primary renal diseases of patients treated for end-stage renal failure in 27 European countries and in Britain.**

Diagnosis	Europe (% patients)	Britain (% patients)
Glomerulonephritis	46.6	46.9
Glomerulonephritis (histologically examined)	(10.0)	(13.1)
Pyelonephritis	19.9	18.0
Drug-induced:		
analgesic abuse	3.3	1.9
Cystic renal disease	8.4	9.9
Hereditary/congenital	3.2	3.1
Renal vascular disease	5.4	6.6
Other identified rare diseases	9.7	10.4
Aetiology uncertain	3.5	3.1
Total no. (%) of patients	47 741 (100%)	6128 (100%)

*Data from all patients recorded on computer files of Registration Committee of the European Dialysis and Transplant Association.²

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nephrosclerosis. This is certainly the largest single contribution that we can envisage for reducing the number of deaths due to end-stage renal disease.

CONGENITAL RENAL DISEASE

There are some patients whose primary renal disease is congenital, and this element probably contributes more patients than the statistics indicate. The proportion of children whose renal failure was attributed to renal medullary cystic disease increased sharply in recent years with a greater awareness of the condition, and now exceeds 10% of all children accepted for regular dialysis and transplantation. Congenital factors, including diabetes, immunodeficiency, and subtle forms of renal dysplasia—as well as the more obvious cystic renal diseases and urinary tract abnormalities—therefore represent a hard core of irremedial conditions resulting in terminal renal failure. When obstructive lesions, gross vesicoureteric reflux, and complicating hypertension have been dealt with then there is little prospect of preventing this group of patients reaching end-stage renal failure.

IMMUNOLOGICAL MECHANISMS

Our knowledge of the fascinating immunological mechanisms underlying glomerulonephritis has grown in the past few years, and we now hope that immunosuppression and plasmapheresis may interrupt these mechanisms in some selected patients. Encouraging early reports have recently appeared of this approach being applied firstly to Goodpasture's syndrome, in which the immunological damage is mediated by antiglomerular basement membrane antibodies, and secondly to systemic lupus erythematosus and rapidly progressive crescentic glomerulonephritis, conditions in which the immunological damage is mediated by soluble immune complexes.¹

Plasmapheresis works by reducing the concentration of circulating antiglomerular basement membrane antibodies or of immune complexes until their production either remits or is inhibited by immunosuppression. Benefit may be due partly to reduction in concentrations of complement and fibrinogen and, in soluble complex disease, partly to passive transfer of high affinity antibody in the purified protein fraction used for replacing plasma volume. Present projections of the usefulness of this treatment predict its value in diseases in which the production of nephritogenic macromolecules is either self-limited or can be controlled by steroids and cytotoxic drugs.

It would, therefore, be rash to hope that these treatments will be useful in more than a few patients with progressive glomerulonephritis. The group to whom they seem to extend the greatest hope of benefit, however, are patients with rapidly progressive forms, of whose tragedy the present-day nephrologist feels so often a helpless spectator. The technique of plasmapheresis is no great hurdle for centres with daily experience of extra corporeal circulation, but it represents a heavy load on blood transfusion services, each treatment needing up to 72 litres of plasma. Assessment of its role as an adjunct to other forms of treatment will depend on the development of simpler and more direct methods for measuring and characterising nephritogenic antibody and circulating soluble immune complexes.

These exciting reports of dramatic success in a handful of patients seem as a faint ripple moving on the vast ocean of end-stage renal disease. Nevertheless, they represent some token of hope from vigorous and costly research programmes into the immunology of glomerulonephritis.

Improving the conservative management of renal failure

Low protein diets ameliorate uraemia, but their use is limited to patients with advanced, stable renal failure. Severe protein

restriction may result in malnutrition. Several groups of workers are at present exploring the use of semi-synthetic diets providing free amino-acids and ketoacids. These can minimise uraemic toxicity and improve nutrition better than diets composed of more normal foods, and they may even offer an alternative to some patients who would otherwise need dialysis. Understanding of the contribution of nitrogen recycling, of the correct balance between essential and non-essential amino-acids, and of the value of ketoacids is likely to improve. Palatability of the synthetic substances must improve if the patient is to agree to a boring diet. For patients with a little residual renal function (GFR 2-5 ml/min) and for whom dialysis and transplantation are inappropriate, these prospects are vital. For other patients diets will prove a temporary phase before embarking on renal replacement treatment and for them the quality of life on the diet must be shown to be as good as, and malnutrition must not jeopardise, their future on regular dialysis.

ACCELERATED ARTERIOSCLEROSIS

Accelerated arteriosclerosis is probably the major unsolved problem affecting the patient on dialysis. Hypertension and raised cholesterol concentrations are clearly common to many patients with renal disease. Lipid abnormalities are particularly likely when the patient passes through a nephrotic stage. In renal failure the concentrations of triglyceride and pre- β -lipoprotein are commonly raised, possibly because of raised plasma insulin concentrations and tissue resistance to its action and possibly because of depression of plasma lipoprotein lipase activity. Corticosteroids given to many of these patients, and notably to those who have undergone transplantation, also raises the plasma triglyceride concentrations. Reports from some of the centres where dialysis and transplantation have been carried out for the longest periods and analysis of the collaborative surveys in Europe and the US make it very clear that an increasing proportion of deaths among these patients is due to vascular disease.

Mortality statistics tell only half the picture, for sub-lethal strokes, incapacitating angina, and ischaemic heart disease add considerably to the morbidity of patients receiving renal replacement treatment. Future management of patients will include investigation of their lipid metabolism and a re-emphasis of the crucial importance of blood pressure control. Whenever possible, these considerations must reach back to the years of conservative management, so that, even if the course of the primary renal disease cannot be altered, at least the secondary consequences of accelerated arteriosclerosis may be averted.

RENAL OSTEODYSTROPHY

The next few years will also see a methodical approach to prevent renal osteodystrophy. A twin-pronged attack on controlling the plasma phosphate concentrations and cautiously titrated vitamin D replacement using new synthetic analogues of active metabolites such as 1 α -hydroxycholecalciferol appears at present to offer a logical approach.

Prospects for improving the conservative management of renal failure add up to a considerable challenge to scientific dietetics. A high calorie diet is needed to spare protein catabolism, but atherogenic lipid concentrations must be reduced. Prevention of renal osteodystrophy demands careful attention to divalent ion metabolism, but the high priority of good blood pressure control and avoidance of hyperkalaemia means that the monovalent ions sodium and potassium must also receive due attention.

Extending renal replacement services

To some extent services for treating end-stage renal disease have been extended by technical innovation. In Britain the major

contribution has been the development of techniques for home dialysis, and two-thirds of patients receiving regular dialysis in Britain treat themselves in their own homes. This technical development was necessitated partly by the threat posed to renal units by serum hepatitis, which led to a policy of patient segregation, and partly because of planning decisions to curtail the opening of new dialysis units. Nevertheless, experience with home dialysis has shown that for many patients self-treatment is a healthier attitude to chronic treatment.

SHORTER PERIODS ON DIALYSIS

In other countries technical innovation, driven by different clinical and economic factors, has moved in other directions.

Satellite dialysis units—In the US and in the Federal Republic of Germany expansion by the development of home dialysis has been superseded by developing satellite, or minimal-care, dialysis units handling large numbers of patients on a quick turn-around basis. The demonstration in these countries, and particularly in Italy, that traditional dialysis schedules of more than 25 hours haemodialysis a week could be shortened has accelerated the adoption of satellite units as the preferred means for making a rapid increase in numbers of patients treated. In Italy short dialysis for 3-5 hours three times a week has been carried out using conventional 1 m² surface area dialysers and a high blood flow (over 300 ml/min) from an efficient arterio-venous fistula.

Large surface area dialysers—In the US there has been considerable interest in large surface area dialysers. This has been a practical extrapolation from the "middle molecule" hypothesis. This hypothesis suggests that some uraemic toxins are of middle molecular size (1000-3000 molecular weight, vitamin B₁₂ with a molecular weight of 1355 being used as a marker), and that their removal by dialysis chiefly depends on the surface area of membrane in the dialyser and the period of dialysis ("square metre hour hypothesis"). The French approach has been to develop a membrane made of polyacrylonitrile, which is especially permeable to these middle molecules.

All these approaches using more frequent, shorter treatment periods have made it possible to reduce total dialysis hours—a welcome advance for the patient—and so make it possible for each treatment station to handle two or even three patients with a double nursing shift. Overnight treatment sessions are giving way to daytime, and especially evening, dialysis schedules. This matches the nursing recruitment needs of less unsociable hours of work.

TECHNICAL DEVELOPMENTS

Two technical developments make it likely that the long-term treatment of patients by peritoneal dialysis will increase. These developments are the permanent indwelling silicone rubber catheter and machine using reversed osmosis to produce sterile dialysis fluid as it is needed and at lower cost than commercially packaged peritoneal dialysis solution.

Portable dialysis equipment—Other interesting technical innovations that will improve the quality of life for the individual patient are under development. The morbidity of dialysis may be ameliorated by carrying out isosmotic ultrafiltration separately from dialysis. Whether this method will be regularly used in short dialysis schedules or reserved for occasions when much fluid must be removed remains to be seen. The use of sorbents combined with ion-exchange resins and urease to regenerate dialysis fluid has made the development of portable dialysis equipment possible. This has opened up new flexibility between hospital and home dialysis by rendering unnecessary the delays and frustrations of home adaptations, and also offers holiday dialysis for the skilled patient. This technology has also made possible the development of an experimental, wearable artificial kidney.

Use of sorbents—There is reason to hope that we stand on the threshold of new treatments based on the clinical use of sorbents. Future prospects include using micro-encapsulated activated charcoal and oxystarch both for haemoperfusion and for the regeneration of peritoneal dialysis solution and also, possibly, as swallowed medicaments that will use the gut to excrete toxins as well. Oral treatment with encapsulated enzymes has also been suggested. In the future, management of patients with end-stage renal disease could involve a combined approach using extracorporeal, peritoneal, and gastrointestinal treatments.

The immediate pressing need, however, is to make renal replacement treatment available to more patients. During 1976, 14.9 patients per million population started treatment in Britain. This is below the average for 27 "European" countries, which was 17.4 new patients per million population. The present arrangement of dialysis facilities in Britain seems to be ripe for introducing satellite units. Home dialysis has been pressed upon our patients to the point of cruelty. Physicians running dialysis services have instances of families wrecked and rehabilitation impaired by the rigours of self-dialysis at home. Units are using precious hospital facilities for the maintenance dialysis of patients who cannot be asked to return to their homes either for medical or domestic reasons and who cannot undergo transplantation.

The number of dialysis centres per million of the population in Britain is 1.0, whereas no other developed European country can boast fewer than 2.0 per million of population. Britain treated 70.4 patients per million of population in 1976, still above the European average of 62.7, but a figure that is bettered by 11 out of the 27 countries who register their patients with the European Dialysis and Transplant Association. Most of those countries supporting more than 100 patients per million of population have at least 3.0 centres per million of population.² The flagging performance of Britain's health services in this area is also related to the few medical staff appointed to work in renal disease.³

TRANSPLANTATION

Prospects for extending transplantation will be dictated by the scarcity of the most necessary commodity—cadaver kidneys suitable for grafting. Society's attitudes rather than the advances of medical science will be the most important constraint. The public can be made increasingly aware of transplantation by the wide dissemination of kidney donor cards both in hospitals and in general practitioners' waiting rooms, and also at such times as when applying for driving licences. The profession will learn through the instruction of present medical students, who (as future junior residents) will have the most opportunities to initiate organ removal. Guide lines for diagnosing brain death have been authoritatively laid down. It is not necessary to pass any new law for this clinical diagnosis to be legally acceptable.⁴ Britain will probably follow other European countries in due course in the adoption of "opting out" legislature.

Much effort will be put into advancing our understanding of the immunology of transplantation. Tissue typing as practiced at present offers only marginal benefits to the recipient of a first cadaver graft. The ability to predict the immune responsiveness of the recipient will help eliminate some of the hazards of organ grafting. Recent re-evaluation by several groups of the effects of blood transfusion on cadaver graft survival may alter the no-transfusion policy widely practised in many dialysis centres. Much more information, however, is required before precise recommendations concerning the quantity, form, and timing of blood transfusions given to dialysis patients awaiting transplantation can be made. Changes in policy must not obscure the data needed to elucidate these points.

Organ preservation—Improvements in organ preservation and in equipment for pulsatile perfusion seem likely. These will facilitate organ transportation and make transplantation more

of an elective procedure than an emergency for the small hours of the morning. Allied to these technical developments will come better tests to predict organ viability. Tests to predict rejection episodes and methods to reduce immunosuppressive treatment are likely to proliferate centre by centre. Further evaluation of the non-immunological factors, age, and clinical state of recipients; their antecedent renal disease and dialysis history; and also the physical condition of the graft should help in optimising these variables.

FUTURE NEEDS

Future prospects for extending renal replacement services appear to have an obvious remedy: more personnel, more renal centres, and more resources. If facilities for treatment are inadequate some patients who could have profited must die. There are no waiting lists. With regular dialysis treatment about half seem likely to have at least 10 years added to their lives, and 80% of survivors on home dialysis will be in whole-time employment. After transplantation the prospects of survival are less good, but the quality of life of the survivors is even better. The replacement of renal function, however, is expensive, if effective, medicine.

It has been sobering to analyse the achievements of different countries in terms of the number of renal patients, both on dialysis and transplanted, whom they were treating on 31 December 1975 (see figure).⁵ The numbers of patients correlate significantly with the per capita gross national product. The US and Sweden provide treatment for rather fewer patients than their respective gross national products would seem able to support. Japan, Israel, and Italy appear to accord greater priority to using resources for this expensive medical endeavour. There is no suggestion that were it possible to measure a country's excellence of medical science or charity of political persuasion these would significantly affect the numbers treated.

Current annual expenditure of Federal Medicare funds for dialysis and transplantation in the US is \$331m.⁶ This provides treatment for almost 30 000 patients with an annual increase of 8000 new dialysis patients and 3000 new renal transplants. Present budgetary arrangements of the NHS do not permit the national expenditure on these items to be identified, but we do know that 2409 patients were on dialysis on 31 December 1976 and that about 600 transplant operations were performed in the year.

Relationship between total number of renal patients (alive on dialysis and with a functioning transplant) and per capita gross national product. Data for 15 individual countries are shown. Regression line was drawn from data from 31 countries, $r=0.821$ and is significant ($P<0.01$).⁵

Therefore, the prospect of treatment for an individual patient who desperately needs expensive renal succour appears to depend on the economic productivity of the society in which he lives. The NHS is at present passing through a phase in which the redefinition of objectives and the planning of services is being dictated by the economic realism of "no growth." It is not uncommon for voices to be raised against the use of resources for expensive renal services. But a society that has decided that, because death from renal failure is easy and cheap, it is also right, must surely be bankrupt.

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What is the treatment for a large inguinal hernia in a middle-aged man?

Without question an inguinal hernia in a middle-aged man should be treated by surgical repair. A truss may be used for temporary relief of symptoms, but it does not prevent the hernia from slowly enlarging, and the patient will have to face operation when older and less fit. In any case, for a truss to be effective and safe the hernia must be completely reducible. If the hernia is not reducible a truss cannot be worn, and there is a greatly increased probability of strangulation. Contraindications to surgery are few and consist of illnesses limiting the patient's life expectancy to a very few years. Respiratory illness, particularly chronic bronchitis, indicates surgery: coughing is much more effective with an intact abdominal wall, and patients can be satisfactorily prepared for operation with antibiotics and physiotherapy. A relative contraindication to surgery is obesity, principally because the fat in the abdominal wall makes the repair more difficult, but these patients are also difficult to fit with satisfactory trusses. In all surgery the obese patient is at a great disadvantage. The size of an inguinal hernia is almost immaterial. Tolerant of a hernia swinging to the knees would be regarded as highly eccentric nowadays. Modern life does not permit it—nor, indeed, do modern trousers. Anything less than this is insignificant in volume compared with the volume of the peritoneal cavity. Most of the worries that used to occur after reduction and repair of these large hernias were due to

inadequate management of the gaseous distension of the gut after a difficult dissection. This would be particularly so if the hernia was obstructed at the time of operation.

Is macrocytosis a side effect of oral contraception?

Serendipity is at work. The last issue of the *British Journal of Obstetrics and Gynaecology* had an article by Chanarin *et al*¹ on the physiological macrocytosis of pregnancy, and the hospital haematologist has been in to inquire whether this could be an oestrogen effect and what about women on the pill? Whether or not oral contraceptives cause folate deficiency, and so macrocytosis, is controversial. Ross *et al*² made a fair survey of the pros and cons, having failed to find any effect of oral contraceptives on serum folate themselves. At the very least there is not a simple cause and effect relationship. All sorts of other factors bear on the matter—iron intake and folate-binding protein for a start. Many of those working on this subject think there is a connection between oestrogen treatment and macrocytosis but are unable to produce a convincing explanation of the mechanism or why it occurs rarely.

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