sufficient vasopressin to raise urine osmolality, thus blurring the expected diagnostic difference. Heavy smoking might also prevent the appropriate shut-off of vasopressin release as the plasma osmolality falls. Clearly, if the kidney cannot secrete a maximally dilute urine excessive drinking will more quickly dilute body fluids.

Body fluids become diluted, then, whenever water is taken in faster than the kidney can excrete it. The excess water is distributed throughout the total body water (about 42 litres in a 70 kg man) and the plasma sodium concentration needs to fall below 120 mmol/l before symptoms are likely; therefore an increase in total body water of at least six litres is necessary before trouble starts. Mild symptoms are best treated by withdrawing water. More severe symptoms, especially the onset of stupor, need treatment with hypertonic saline. This is given most conveniently as 5% saline (855 mmol/l) at a rate of 1 ml/min until improvement occurs. Though it is rarely necessary to give more than 250 ml of 5% saline, even that small volume will extract a substantial quantity of water osmotically from the intracellular into the extracellular space

—and this substantial increase in the plasma volume may be enough to precipitate heart failure and pulmonary oedema in susceptible people. In practice this danger is partly offset by the tendency of these patients to excrete a sodium load rapidly in the urine. In patients in whom heart failure seems a strong possibility the combination of frusemide (which produces a dilute urine in patients with hyponatraemia) and a slow infusion of hypertonic saline may be more appropriate.⁸

Once the urgent biochemical emergency has been overcome psychiatric treatment should be arranged in an attempt to prevent a recurrence of this dangerous syndrome.

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Regular Review

Current trends in the treatment of uraemia: a view from the United States

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In the 35 years since Willem Kolff first attempted to correct the complex metabolic disturbances of uraemia by simply circulating blood through Cellophane membranes, effective treatment of end-stage renal disease has become a routine part of clinical medicine. In the United States alone some 40 000 people are now on dialysis, and 27 000 others have received kidney transplants in the last decade.

Some 10 000 Americans develop renal failure each year, reflecting an incidence of 50 per 100 000 population. Increasingly liberal criteria for haemodialysis, freely available as a Medicare benefit since 1973, have resulted in the acceptance of many patients who are old or suffer from diabetes, heart disease, or cancer; and heroin addicts, convicts, and blind diabetics are also being treated.

For most patients receiving *haemodialysis* life has become less difficult than in the early days; and the estimated mean of 22 days in hospital each year obscures the fact that many patients have been treated for years without ever having been admitted. Patients on dialysis are surviving increasingly longer, especially if allowance is made for the many individuals who are debilitated or have serious medical problems. Since 1973 the proportion of patients treated in free-standing facilities has increased, and that of home dialysis has declined from 40% to about 15%, the considerable regional differences being variously attributed to lack of incentives, the bias of physicians, patients' preference, and the population's heterogeneity.¹

Some nephrologists believe that the place of dialysis is in the home and that as many as 70% of all patients should be able to perform self-dialysis.¹ A more realistic proportion, however, is probably 20%,² and even this may be too high for centres treating patients from the ghettos of the inner city; older people; and those with major medical, psychological, or social problems²—while retrospective comparisons claiming higher survival rates and better rehabilitation in home patients are often hampered by selection bias.³ An interesting approach, however, recently tried in some parts of the country, has been to pay nursing aides to dialyse patients in their own homes—possibly a happy medium between centre and home dialysis, but not necessarily much cheaper.

For the patient on haemodialysis access to the vascular system remains his lifeline as well as his Achilles' heel. Most patients are treated through a standard Brescia-Cimino fistula, constructed several weeks before it is needed, or initially through a Scribner shunt, which may later be converted into a fistula. For patients whose fistulas have failed the bovine heterografts used since 1972 are being largely supplanted by expanded polytetrafluorethylene (PTFE) grafts, which are cheaper and more easily handled, can be used earlier, are less prone to clot, and when infected may be salvaged by antibiotic treatment.^{4 5} Most patients are treated by a two-needle puncture technique, but for difficult cases single-needle systems are available, though rarely used.

The dialysis systems are either of the batch or of the proportioning type, and the water used is now almost always deionised. Many centres use glucose-free dialysate, and some have increased the sodium concentration in the dialysate to avoid cramps during ultrafiltration. In the future acetate may be replaced by bicarbonate, especially for high-flux dialysers, to avoid incomplete correction of metabolic acidosis, cardiovascular instability, or excessive generation of triglycerides. All centres use disposable dialysers, of the coil, hollow-fibre, or flat-plate varieties, with surface areas ranging from 0.8 to 2.5 m² and with varying membrane thickness. Though the price of dialysers has come down in recent years there remains much interest in reusing them, and feasibility studies are in hand. Most centres dialyse patients for four hours thrice weekly, and many are experimenting with the technique of sequential haemodialysis-ultrafiltration in a single session to remove large amounts of fluid without inducing hypotension. Haemodiafiltration, where plasma is subjected to ultrafiltration and reconstituted with saline, is a novel approach to removing solutes that is still confined to a few centres. Even further down the line in the treatment of uraemia is haemoperfusion, a procedure at present reserved for cases of drug intoxication. But sorbent dialysis using a small volume of dialysate (1-5 litres) and a cartridge containing urease, zirconium, and charcoal is widely used in the popular Reddy system, which being portable lends itself to acute dialysis in small hospitals. Even more portable are a variety of wearable or suitcase kidneys, which allow the patient to dialyse in hotel rooms, movable caravans, and "primitive recreational areas."

In the everyday management of patients on haemodialysis fluid overload from non-compliance often remains a problem. In most cases hypertension responds to ultrafiltration and conventional drugs; but in refractory cases minoxidil or ultimately bilateral nephrectomy may be needed. Patients are encouraged to work, to eat well, and to take water-soluble vitamins, folic acid, and phosphate-binding agents. Iron is given orally, sometimes intravenously; but its rational administration must await the more widespread availability of the ferritin assay. Pruritus is treated with limited success by emollients, antihistamines, tranquillisers, and (increasingly) ultraviolet light—rarely by subtotal parathyroidectomy or intravenous lidocaine. Pericarditis often clears with increased dialysis time, sometimes supplemented by oral indomethacin or intrapericardial triamcinolone, but may require surgery. Among other complications are viral hepatitis, still an unconquered problem; staphylococcal infections, often treated by weekly intravenous vancomycin; intractable ascites, sometimes requiring a LeVein shunt; tuberculosis and endocarditis, often insidiously progressive and difficult to diagnose; and a whole host of endocrine and metabolic complications. The treatment of bone disease is in a state of flux because 1,25-dihydroxycholecalciferol has only recently become available. Zinc deficiency has been implicated as a cause of loss of taste and of impotence, and its absorption may be facilitated by vitamin D. The epidemic form of dialysis dementia appears to be related to aluminium, but sporadic cases continue to baffle the investigator. The advent of cimetidine has been a great boon in the treatment of peptic ulceration and haemorrhage; while hypertriglyceridaemia may be alleviated by using a glucose-free dialysate or occasionally drugs. The propriety of embarking on major reconstructive coronary artery surgery remains a subject for debate.

Peritoneal dialysis is often advocated as a viable alternative to haemodialysis, but it is used in less than 3% of all patients.¹ It is largely reserved for acute renal failure, for the initial

period of evaluation of patients with chronic renal failure, for those with access problems, and for elderly patients with diabetes or cardiovascular instability. Loss of protein in the dialysis fluid, though an important consideration, pales into insignificance compared with the problem of infection. Some help has come from a variety of automated devices and closed systems, so that a few patients are now successfully treated at home. Methods of increasing the clearance of the peritoneal membrane by using a variety of drugs are of great interest but remain in the experimental stage. More promising is continuous ambulatory peritoneal dialysis (CAPD), in which the patient carries a plastic bag at his side and exchanges eight litres of fluid per day while going about his usual business.⁶ In the United States the use of plastic bags has only recently been approved by the Food and Drug Administration, and a multicentre evaluation of this technique is being planned. Another interesting development is a sorbent-regenerated dialysis system using only 3.6 litres of fluid in a two-catheter continuous-flow system.

The number of *renal transplants* in the United States has not increased appreciably in the last few years¹—even though the criteria for selecting patients for transplantation have been relaxed so that older patients and those with diabetes and "cured" malignancy are being considered. At present cadaver donors provide some 70% of all kidney transplants. Cadaver kidneys are usually maintained by cold pulsatile perfusion if transplantation is to be delayed by two or three days, but are stored in cold Collins's solution if the transplant is done within 24 hours. Unlike the experience in Europe, HLA matching between donor and recipient has not improved the survival of cadaveric grafts in the United States, though recently the Iowa University group⁷ has published data showing better results with good HLA matching. Graft survival is now believed to be enhanced in recipients who have had transfusions of whole blood or packed cells before transplantation, the effect being particularly striking if more than 20 units of transfusion have been given. Frozen blood seems to lack this effect.⁸

Acute rejection episodes are handled by a three-day course of intravenous pulse therapy with 1 g methylprednisolone daily and local graft irradiation. The value of antilymphocytic globulin for preventing rejection has been controversial, perhaps because of the difficulty in preparing consistently immunosuppressive batches. High doses may reduce the patient's survival because of an increased infection rate, this being particularly true in the older patient. Antilymphocytic globulin is probably of no value for grafts from live related donors⁹⁻¹¹; but specific antithymocyte globulin may prolong cadaveric graft survival.² Baseline and subsequent technetium and hippuran renal scans are regularly used to diagnose graft dysfunction, and biopsy of the graft to diagnose rejection or recurrence of the original disease. At present the two-year functional graft survival is 70-75% for sibling transplants and 40-45% for cadaver kidneys.¹² The survival rates of the grafts have not improved in the last decade because more high-risk patients are being transplanted, and because less aggressive immunosuppressive treatment is used in the hope of increasing the survival of the patients.

Among the complications of transplantation infection remains the most common and accounts for most deaths, but its incidence may be reduced by less aggressive immunosuppression, more attention to aseptic technique, more widespread use of ultrasonography and gallium scans for detecting collections of fluid and inflammatory sites respectively, perhaps the perioperative use of wide-spectrum antibiotics,¹³ and (in the future)

selective immunosuppressive techniques such as treatment of recipients with cell-free donor antigens or antidonor (enhancing) antibodies.¹¹ Of great concern is a 5-6% incidence of neoplasms in transplant recipients (100 times greater than in age-matched controls), skin cancer and lymphomas (often affecting the brain) being the most common. Up to 15% of the recipients of transplants develop aseptic bone necrosis,² and parathyroidectomy is sometimes needed for relentless osteodystrophy. Recurrence of the original disease occurs in 15% of transplants (but in 40% of patients with dense deposit disease); but it may be manifested by proteinuria only and does not necessarily result in graft failure.² Other complications are cataracts, Cushing's syndrome, diabetes, and peptic ulceration; while the main long-term causes of death are pneumonia, chronic hepatitis, and cardiovascular disease.¹¹

It has long been a truism that renal transplantation and dialysis are complementary and not competing forms of treatment. Yet the controversy continues to rage about which is the preferred method of treatment. While here again most reports on survival and rehabilitation suffer from selection bias—since younger and healthier patients are usually offered transplantation—few people would deny the superiority of living donor transplantation, with its two-year survival rate of 85% for recipients of grafts from siblings and 80% for those with grafts from parents.¹² For most patients, however, the issue resolves itself into choosing between dialysis and cadaver transplantation. At present dialysis offers an 80% survival rate at two years, with a subsequent death rate of 10% per year; while for cadaver transplantation the two-year functional graft survival rate is about 45% and the mortality rate is 35%.¹² If recent reports of a 5% first-year death rate can be substantiated¹³ then cadaver transplantation will become an attractive alternative, but graft survival still has to be improved. Meanwhile young patients on dialysis who cannot obtain a graft from a living relative should at least be offered the chance of considering cadaver transplantation.

For children over 5 years of age and adolescents transplantation offers better prospects for rehabilitation than dialysis.

Children generally do as well as adults with parent-to-child or cadaver grafts, but under 5 years recipients of cadaver grafts do poorly, and the results are even worse for children under the age of 2.¹¹ Another special category is the juvenile diabetic, who frequently fares badly with whatever method of treatment he is offered. Somewhat more favourable results, however, have been reported from the University of Minnesota, where early transplantation is advocated in the hope of arresting the progression of vascular degeneration and neuropathy.¹⁴

The first-year cost of a cadaver graft is estimated at \$25 000, and that of a second one at \$20 000,¹⁵ excluding the cost of treating rejection, follow-up visits, and admission to hospital for complications of transplantation. For haemodialysis the annual cost per patient is \$25 000 in hospital units, \$20 000 in limited-care facilities, and \$15 000 in the home. The entire cost of the uraemia programme already exceeds one thousand million dollars per year, or 5% of the nation's Medicare budget, and it may double by 1981. Current efforts to reduce costs, centred on promoting home dialysis and transplantation, were embodied in recent legislation providing financial incentives for these types of treatment. But while the effect of these measures remains to be determined, the inexorable rise in the cost of this single-category programme has not escaped the notice of politicians struggling with the issue of comprehensive national health insurance. Meanwhile less than 1% of the money spent on treating end-stage renal disease has been allocated to research; yet much remains to be learned if we are to prevent renal failure, liberate man from machines, and unravel the tangled web of uraemia.

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