The kidneys are responsible for the excretion of nitrogenous waste products and the elimination of the non-volatile acids produced by metabolism. Through selective reabsorption of the bulk of the glomerular filtrate, they regulate the volume and composition of the body fluids. Because of the part they play in the control of sodium balance and in the production of the enzyme renin, they are intimately concerned in the regulation of blood pressure. As the main source of the hormone erythropoietin, they are essential to normal red blood cell production. In view of the variety and importance of the tasks performed by the kidneys, it is not surprising that when renal failure supervenes the effects are manifest in practically every system of the body.

**CLINICAL FEATURES AND COMPLICATIONS OF CHRONIC RENAL DISEASE**

Disturbances in Water and Electrolyte Balance.

Loss of concentrating ability occurs early in the course of renal disease. The circadian rhythm of salt and water excretion is abolished, and nocturia is an almost universal symptom.

Salt and water.

About 10 per cent of patients with chronic renal disease are unable to conserve salt and water (Atkins, Leonard and Scribner, 1971). Usually, but not invariably, these patients have conditions such as chronic pyelonephritis, analgesic nephropathy, or polycystic renal disease, where the distal nephron is primarily affected, and tubular damage is out of proportion to the degree of glomerular injury. Patients with salt-wasting renal disease tend to be normotensive or slightly hypotensive. They are seldom oedematous. Renal function in such patients can be improved by a high intake of salt and water; a component of their uraemia is prerenal and therefore correctable. Any intercurrent illness (e.g. gastroenteritis) which reduces the intake of fluids and electrolytes or increases their loss from the body, can lead to a rapid worsening of the uraemia.

Patients who have a tendency to retain sodium occur more frequently than patients with salt-wasting renal disease. These patients tend to develop intractable oedema, and are readily precipitated into congestive cardiac failure. They are usually hypertensive, and blood pressure often is difficult to control. In such patients, the effects of renovascular damage from hypertension are added to those of the original renal disease, and there is a tendency for renal function to decline—gradually as a rule, but sometimes suddenly as a result of accelerated hypertension.

**Water.**

The ability to dilute the urine is preserved for longer than renal concentrating ability and thirst mechanisms are intact in patients with renal disease. Pure water depletion and pure water excess are therefore much less common than retention or loss of salt and water together. When pure water im-balance does occur, however, it can usually be diagnosed from inspection of the serum sodium concentration. A serum sodium of 145 m.equiv/l. or more is almost always indicative of pure water depletion, while a serum sodium of 130 m.equiv/l. or less is indicative not of sodium depletion but of water excess (Burnell, Paton and Scribner, 1960). Water intoxication may be induced iatrogenically by over-enthusiastic efforts to improve renal function by pushing fluids. Cerebral oedema may ensue, with headaches and convulsions. The latter may prove fatal.

Potassium.

When renal function is markedly diminished, the kidneys are unable to cope with sudden large oral loads of potassium or with the release of potassium from rapid cell breakdown. Hyperkalaemia interferes with the excitability of nerve and muscle cells. The patient may complain of paraesthesiae and muscle weakness, but often the first and only sign of potassium intoxication is cardiac arrest.

Potassium depletion is occasionally seen, particularly in patients with salt-wasting syndromes. Hypokalaemia produces lethargy and muscle weakness. It also causes renal damage. There is swelling of renal tubular cells in association with very marked...
impairment in renal concentrating ability. Thirst and polyuria occur, and large amounts of dilute urine may be produced in conjunction with a rise in blood urea. If potassium depletion is not corrected, the interstitium becomes infiltrated with inflammatory cells, and this is followed by fibrosis of the interstitium.

**Acidosis.**

While carbonic acid can be excreted by way of the lungs, other acidic products of metabolism must either be excreted by the kidneys or buffered within the body. Patients with renal failure of any severity usually have a degree of metabolic acidosis. Classically this is associated with rapid, deep breathing of the type known as "Kussmaul's respiration". The presence and degree of this sign, however, is not dependent solely on the degree of acidosis, but is influenced also by the rate at which acidosis has developed.

From studies conducted by Relman (1968) it would appear that the average low protein diet gives rise to about 45 milli-equivalents of fixed acid daily, and that patients with glomerular filtration rates in the range 5–10 ml/minute are able to eliminate about 25 milli-equivalents of hydrogen ion in the urine each day (Relman, 1968). Thus most patients with severe chronic renal failure are permanently in positive hydrogen ion balance. The plasma bicarbonate, however, does not fall progressively with time, but tends to stabilize at around 12–15 m.equiv/l. It has been suggested that in stable chronic renal failure hydrogen ions are taken up by bone in exchange for calcium ions (Relman, 1968).

In acidosis, positively charged hydrogen ions enter cells, and (for reasons of electrical neutrality) potassium ions are displaced into the circulation. If this happens gradually, the danger of severe hyperkalaemia is slight. Respiratory obstruction, however, by adding a respiratory component to the metabolic acidosis already present, can precipitate a dangerous rise in the serum potassium. The apnoea which frequently complicates grand mal convulsions and occasionally occurs during the induction of anaesthesia can sometimes prove fatal, for the same reason.

**Hypertension.**

Patients with renal disease can usefully be divided into those in whom hypertension is either absent or readily controllable, and those in whom it is severe and resistant to therapy. Patients in the former group can, generally speaking, be managed conservatively for a considerable time. Where hypertension cannot be adequately controlled, however, the renal disease tends to proceed relentlessly in a downhill direction.

In the majority of patients with hypertension and renal failure, the hypertension appears to be secondary to salt and water retention. This can be seen from studies on patients maintained on the artificial kidney. In the majority of patients on long-term dialysis, the blood pressure can be titrated against the salt and water content of the body, and sodium depletion will usually lead to control of the blood pressure (Comty et al., 1966; Thomson et al., 1967). In a relatively small number of patients, the blood pressure cannot be controlled by sodium depletion, but is improved by bilateral nephrectomy. It is thought that in this small group of patients, and in this group only, overproduction of renin is the major factor in the perpetuation of hypertension (Brown et al., 1971).

Patients in whom the hypertension is clearly sodium-dependent do not show any clear relationship between the height of the blood pressure and the concentration of circulating renin. Patients who do not respond to salt depletion, but who are ultimately improved by nephrectomy, do show a clear correlation between the degree of hypertension and the concentration of renin in the blood (Vertes et al., 1968).

Because of the frequency with which hypertension is encountered in patients with renal disease, the complications of uraemia include those of uncontrolled hypertension. Headaches, retinopathy, and left ventricular failure are common in chronic renal failure, while hypertensive encephalopathy may present with convulsions, coma, or a variety of other neurological signs.

**Pulmonary Complications.**

Pulmonary oedema is so common in renal failure that the term "uraemic lung" is often employed to describe congestive changes seen in the lung fields of patients with severe renal disease. This pulmonary oedema is often associated with pulmonary artery pressures which are in the normal range (Gibson, 1968). In left ventricular failure, the pressure in the pulmonary arteries is almost always raised. Although "uraemic lung" can be controlled by salt and water restriction, it would appear that both overhydration and increased pulmonary capillary permeability play a part in its inception (Merrill and Hampers, 1971).

Chest infections are relatively common in uraemic patients, and pulmonary infarction can also occur.
The appearance of a pleural friction rub and a pleural effusion is not always due to one or other of these causes, however. A fibrinous pleuritis with a friction rub may appear in the absence of infection or embolism. This condition has been regarded as the pleural analogue of uraemic pericarditis (Nidus et al., 1969).

**Skin Manifestations.**

Urea frost is described in many of the more vulnerable accounts of renal failure, but is in fact uncommon in the presence of adequate hygiene.

Pigmentation is a constant finding in uraemia. It is due partly to an increased deposition of melanin in the skin, and in part to retention of urochromes normally excreted in the urine. Pigmentation tends to be more intense in severely uraemic patients and patients inadequately dialyzed than in those whose metabolic state is more adequately controlled by frequent dialysis (Blainey, 1968). It is sometimes particularly striking in patients with severe salt-wasting syndromes.

Pruritis can be both distressing and intractable. In a minority of patients it is due to secondary hyperparathyroidism. The itching is due to deposition of calcium phosphate in the skin, and can be relieved by parathyroidectomy (Hampers et al., 1963). In most cases, the cause is more obscure. Control of the biochemical state will usually lead to improvement in this symptom, but relief is not invariable.

Brusing of the skin is a reflection of the bleeding tendency which occurs in uraemia. This bleeding tendency will be discussed in detail later.

**Gastro-intestinal Features.**

Salivation is reduced in uraemia, and mouth breathing is usual. The oropharynx can become very dry. This makes oral hygiene difficult, and mouth ulceration or even parotitis may occur. Nausea and vomiting are common, while diarrhoea, though an inconstant feature, may be profuse and sometimes bloody. These symptoms are improved, sometimes dramatically, by very low protein diets of the type introduced by Giovanetti (Berlyne and Hocken, 1968). Antibiotic cocktails which act to sterilize the gastro-intestinal tract also lead to improvement in anorexia, nausea, and vomiting (Wrong, 1967). These observations are consistent with the view that these symptoms may be caused by the breakdown of large amounts of urea to ammonia by gastro-intestinal bacteria (Merrill and Hampers, 1971).

**Neurological Complications.**

Disturbances of consciousness occur in uraemia, and range from mild drowsiness to deep coma. Psychiatric changes are also prevalent. These may take the form of mild disorientation or present as severe psychoses (Tyler, 1968).

Hypertensive encephalopathy can affect almost any part of the brain. Hypocalcaemia may give rise to tetany and convulsions. Drowsiness, headache, and convulsions can also result from cerebral oedema. Swelling of intracranial cells can be produced by water intoxication following excessive fluid intake, or follow sudden changes in biochemistry such as are produced by dialysis. Dialysis tends to remove urea from the blood more rapidly than urea can diffuse out of cells. This leads to an osmotic shift of water from the extracellular space into the intracellular compartment (Kennedy et al., 1963).

In addition to above features, a clinically detectable peripheral neuropathy is present in approximately 50 per cent. of severely uraemic patients (Nielsen, 1967). The mode of presentation varies. In some cases the patient experiences an unpleasant sensation which is often relieved by moving the legs or walking about (Callaghan, 1966). In others, the "burning feet syndrome" may occur. This consists of hyperaesthesia of the lower limbs in association with marked vasodilatation (Tyler, 1968). Usually the patient has no specific neurological complaints, and neuropathy is suspected on the grounds of bilaterally impaired deep reflexes in association with impaired vibration sense. These changes are most marked in the lower limbs (Nielsen, 1967). Confirmation of the diagnosis is obtained by measuring nerve conduction velocities. These are markedly reduced in uraemic neuropathy. Measurements are best carried out in the lateral popliteal nerve (Jennekens Most et al., 1969). Uraemic neuropathy develops when the metabolic abnormalities of renal failure have been present in severe form for a considerable time. Before the advent of long-term dialysis therapy patients usually died before they became incapacitated by this complication. In the early days of long-term dialysis when patients were dialyzed as little as possible and remained alive but severely uraemic, florid and incapacitating neuropathy became distressingly common (Lindholm, Burnell and Murray, 1963). It is now standard practice for haemodialysis to be carried out at least twice weekly for the total period of at least 28–30 hours, and severe neuropathy is once more becoming rare.
Involvement is peripheral rather than central, and the lower limbs are affected more than the upper. Nerve biopsy shows segmental demyelination with secondary axonal degeneration (Jennekens, Most van Spijk and Dorhout Mees, 1969).

**Uraemic Myopathy.**

Myopathy is relatively rare in renal failure. When it occurs it is as a complication of uraemic osteodystrophy (Stanbury, 1967; Floyd et al., 1969). It can be distinguished from uraemic neuropathy by the fact that weakness is confined to the proximal muscles. Unless neuropathy coexists, sensory changes are absent, and deep reflexes are well preserved even when muscle weakness is severe. If treatment of the osteodystrophy is successful muscle weakness rapidly improves.

**Uraemic Osteodystrophy.**

Metabolic bone disease takes years to develop in renal failure. The bones of adults dying of renal disease were known many years ago to be abnormal histologically (Follis and Jackson, 1943) but disability due to bone disease did not become clinically important in adults until the advent of long-term haemodialysis. The situation is somewhat different in children; disorders of calcium metabolism make their presence felt at an earlier stage when the skeleton is actively growing, and "renal rickets" has been recognized in children for over fifty years (Barber, 1921).

The complex subject of metabolic bone disease in renal failure has been well reviewed by Stanbury (1967) and by Siddiqui and Kerr (1971). This present account is oversimplified to some extent.

The prime cause of renal osteodystrophy is the resistance to the actions of vitamin D which is universally found in patients with renal failure (Lumb, Mawer and Stanbury, 1971). This leads, inter alia, to severe impairment of calcium absorption from the gut.

As a result the serum calcium level tends to be low. Because of the lowered glomerular filtration rate, serum phosphate levels are high. Both these factors stimulate the parathyroid glands to secrete parathyroid hormone, and all patients with chronic renal failure have markedly elevated levels of this hormone in their blood (Berson and Yallow, 1971). Although parathormone secretion is increased in all patients with renal failure, the biological effects of this hormone are apparent in only a proportion of patients. In the patients where parathormone appears ineffective, the serum calcium level remains low. Tetany may occur. The bone lesions which ultimately appear are those of osteomalacia.

In the patients where parathormone acts effectively, the serum calcium level rises towards normal, mainly as the result of calcium mobilization from bone. These patients show the bone lesions of osteitis fibrosa cystica. In the presence of renal failure, parathormone is unable to increase phosphate excretion, and the serum phosphate level remains high. The serum (calcium × phosphate) product thus becomes elevated, and deposition of calcium and phosphate tends to occur—in blood vessels, in the skin, in the eye, and elsewhere. When metastatic calcification occurs in bone, localized areas of osteosclerosis appear on bone radiographs.

In practice, the bone lesions are not clear-cut. While the lesions of osteomalacia predominate in some patients and those of osteitis fibrosa in others, there is considerable overlap. Both types of bone lesion can frequently be seen in the same patient, with or without the addition of areas of osteosclerosis.

A further complication can ensue if the hyper trophyed and hyperactive glands become autonomous. Here the serum calcium becomes higher than normal, and the bone lesions of hyperparathyroidism become increasingly severe. This situation is sometimes termed "tertiary hyperparathyroidism".

A further form of metabolic bone disease in renal failure has been described in Newcastle (Siddiqui and Kerr, 1971). This consists of progressive osteoporosis, with bone pain and pathological fractures. The cause of this condition is unknown. It occurs only in patients who are on dialysis therapy and is common in some dialysis centres but unknown in others. A correlation has been noted between this form of bone disease and a high fluoride concentration in the dialysis fluid (Siddiqui et al., 1970).

**Uraemic Pericarditis.**

Uraemic pericarditis was once regarded as a harbinger of doom. Wacker and Merrill (1954) found the average survival in uraemic patients from the onset of pericardial friction to be only 10 days. With the advent of long-term haemodialysis, prolonged survival following the development of pericarditis is now quite common. This complication did, however, account for 6 per cent of 500 deaths in patients on long-term dialysis in Europe during 1968–69 (Drukker et al., 1969).
Uraemic pericarditis is characterized by relatively severe pain which is usually pleuritic and which is frequently influenced by posture. The electrocardiograph is unhelpful; in one series of 25 cases it indicated the correct diagnosis in only 6 (Beaudry, Nakamoto and Kolff, 1966). Pericarditis in uraemia may be complicated by haemorrhage into the pericardial sac, with consequent tamponade. This is particularly liable to occur when patients are heparinized for the purpose of dialysis (Tenckoff et al., 1965). Most adequately dialyzed patients who escape death from tamponade recover from pericarditis without sequelae, but chronic constrictive pericarditis occurring months or years after the resolution of an acute episode has been reported (Lindsay, Crawley and Calloway, 1970).

Renal Anaemia.
In severely uraemic patients anaemia is universal. The aetiology of this anaemia is multifactorial. Severe uraemia leads to a generalized bleeding tendency, to haemolysis, and to toxic depression of the bone marrow. All these factors can be corrected by dialysis.

Long-term haemodialysis, however, itself contributes to anaemia. Loss of blood into the machine during dialysis can produce iron deficiency. Folic acid deficiency may also develop. The vitamin is dialyzed out of the body, and the diet may not be adequate to make good this loss (Wright, Goldsmith and Hall, 1968; Hampers et al., 1967).

Even when the uraemic state is adequately controlled by dialysis, and deficits of iron and vitamins are fully corrected, anaemia persists. In the absence of normal renal tissue, the hormone erythropoietin is not produced in adequate amounts. The bone marrow appears to have a basal rate of red cell production, even in the absence of erythropoietin, but without this hormone the haemoglobin level does not rise above 7–9 g per 100 ml (Jacobson et al., 1957; Eschbach et al., 1967). Following a successful renal transplant there is an immediate reticulocytosis and a rapid rise in haemoglobin to normal levels.

Disorders of Coagulation.
A generalized bleeding tendency is common in severe uraemia. Epistaxis and severe bruising are frequent manifestations. There appear to be two components to the bleeding tendency. There is some increase in capillary fragility, and there is a functional platelet defect characterized by reduced platelet stickiness (Eknoyan et al., 1969). These abnormalities have been linked with retention of guadino-succinic acid (Stein, Cohen and Kornhauser, 1969). The bleeding disorder of uraemia is rapidly corrected by dialysis (Von Kaula et al., 1966).

CONSERVATIVE THERAPY IN CHRONIC RENAL FAILURE

Diet.
Many of the features of uraemia arise from the retention of nitrogenous waste products. These features can be alleviated to a useful extent by restricting the dietary intake of protein. In order to minimize the breakdown of body cells, it is important that protein restriction be accompanied by the intake of at least 2,000 and preferably 3,000 calories per day.

Protein restriction does not slow the progression of renal damage, and is only of value in reducing the accumulation of metabolic waste products. Until this accumulation reaches a significant level, there is therefore no point in reducing the protein content of the diet.

The precise amount of protein which should be given to patients with chronic renal failure is still a matter of debate. It is important to provide a balanced diet; patients with uraemia have enough to contend with without the added trials of iatrogenic malnutrition. The protein intake must be enough to prevent or minimize the development of a negative nitrogen balance, as this produces gross muscle wasting and may contribute to the development of neuropathy and cardiomyopathy.

Some workers have suggested that nitrogen balance can be maintained on an intake of protein which is as low as 0.25 g per kg body weight—provided that over 90 per cent of the dietary protein is first class (Giovanetti and Maggiore, 1964; Berlyne and Hocken, 1968). Others have found that considerably more is required to prevent protein malnutrition, and have suggested a protein intake of 0.4–0.5 g per kg (Herndon, Freeman and Cleveland, 1958; Ford et al., 1969). Very low protein diets of the Giovanetti type, from which second-class protein is excluded, are unpalatable and difficult to administer. Such diets lead to improvement in some features of the uraemic syndrome, particularly those involving the gastro-intestinal tract. Other aspects, such as the development of neuropathy and pericarditis, are not influenced.

It has recently been shown that in most uraemic patients at least 0.4 g of protein per kg of body
weight is necessary to maintain nutrition, and that with protein intakes of this order, the inclusion of second-class protein as part of the allowance has no deleterious effect—provided the proportion of first-class protein included does not fall below 40 per cent (Ford et al., 1969). Current opinion is thus tending to swing away from the complexity of the Giovanetti diet to simpler and more palatable "ordinary" low protein diets.

Once the blood urea has reached the range 130–170 mg/100 ml and protein restriction becomes necessary, 0.5 g of protein per kg of body weight should be given, and 60 per cent or more of this should be first-class protein of animal origin. If there is significant proteinuria, additional dietary protein should be given to make up for the urinary loss (Blainey and Chamberlain, 1971).

Assessment of Fluid and Electrolyte Requirements.

Patients with renal failure differ widely in their salt and water requirements, and the same patient may have varying needs at different times. The optimum intake of sodium, bicarbonate, potassium and water has to be determined empirically for each individual.

If the patient is normotensive and does not have oedema, the presence of a salt-wasting syndrome is a distinct possibility. A high fluid intake should be given initially, along with sodium chloride and sodium bicarbonate supplements. The patient's weight and blood pressure should be carefully observed, and the electrolytes estimated daily. Fluid balance charts should be carefully kept. If the weight increases steadily, the patient is obviously retaining sodium, and the sodium intake should be cut. If the serum sodium falls to below 130 m.equiv/1., the intake of water is obviously excessive, and this should be reduced.

If, on the other hand, the patient is hypertensive and oedematous, the sodium content of the diet should be cut to about 20 m.equiv/day. Oedematous patients often have difficulty in handling a water load, so the fluid intake should be limited to 500 ml plus the volume of the previous day's output. The urinary sodium excretion on this regime should be measured. If it is found that this does not fall below (for example) 60 milli-equivalents daily, the dietary intake of sodium should be increased to this amount—once the oedema and hypertension have been corrected. Even patients who have oedema at the time of presentation tend to have an obligatory leak of sodium in the urine. If this obligatory excretion is not taken into account, salt and water depletion may ultimately ensue, with a consequent decline in renal function.

The Management of Hypertension.

Control of blood pressure in patients with renal disease is often difficult, but is always essential. Uncontrolled hypertension not only exposes the patient to the risk of complications such as cardiac failure, blindness, and hypertensive encephalopathy, but also hastens the decline of renal function.

Many patients respond adequately to methyldopa, possibly with the addition of hydralazine. Where postural hypotension is a problem, and where cardiac failure is not a feature of the condition, beta-blockers are worthy of a trial.

Hypertension in renal disease is intimately bound up with problems of sodium balance. Dietary sodium restriction will almost always make the blood pressure easier to control. Sometimes, however, the sodium excretion is so minimal that a diet sufficiently low in sodium cannot be devised. In addition it may be found that if the sodium intake is reduced to a level at which the hypertension is controlled, the glomerular filtration rate declines alarmingly. In difficult cases of this kind, it is often found that management is made easier by the addition of frusemide in high dosage to the regime. This increases the excretion of sodium and facilitates dietary control of sodium balance (Atkins, Leonard and Scribner, 1971). Hypertension in patients with renal failure often enters a malignant phase. When treatment is a matter of urgency, diazoxide, 300 mg intravenously, is often the therapy of choice. It may be worthwhile continuing diazoxide therapy twice daily for several days, as there is evidence to suggest that if the blood pressure is held in the normal range for an appreciable time, subsequent control may become easier (Thurm and Smith, 1967). As diazoxide causes hyperglycaemia, it should not be used on a regular basis for more than 10 days.

The Management of Cardiac Failure.

This usually results from uncontrolled hypertension and fluid retention, and tends to respond to salt and water depletion (by dialysis if necessary) and control of the blood pressure. Digoxin is also of benefit, but the dosage of this drug must be adjusted in the presence of renal failure. The digitalizing dose is the same as in patients without renal disease, but for maintenance therapy dosage should be less than 50 per cent of normal. In many patients 0.25 mg of
of patients with renal failure. They increase protein breakdown, and can induce a severe worsening in the uraemic state (Edwards, Huskisson and Taylor, 1970).

Treatment of Uraemic Neuropathy.
This is a complication of inadequate dialysis or of conservative therapy which has been persisted with for too long. It can be prevented by instituting dialysis in those patients selected for this form of treatment before the serum creatinine has risen to 15 mg/100 ml, and by ensuring that dialysis, once started, is carried out with adequate blood flows for a minimum of 14 hours twice a week.

In patients with established neuropathy, adequate dialysis will usually lead to the relief of sensory disturbances within a few weeks. Motor neuropathy is more intractable, and may take months or years to improve (Merrill and Hampers, 1971).

The Treatment of Uraemic Pericarditis.
If dialysis is instituted early and carried out vigorously, this complication too can be prevented. Once pericarditis has developed, dialysis therapy should be started forthwith, if this therapy is appropriate and available. Routine heparinization for the purposes of haemodialysis should be avoided because of the very substantial risk of inducing haemopericardium and tamponade. Regional heparinization should be employed instead. This involves the adding of heparin to the blood entering the artificial kidney and protamine to the blood leaving it. The infusion rates of the two solutions are adjusted so that the machine is heparinized but the patient is not. Dialysis should probably be carried out thrice weekly for a month or six weeks, as strict biochemical control seems to hasten healing in pericarditis.

Paracentesis can initiate bleeding, and should probably be reserved for those cases showing evidence of tamponade. If haemopericardium is persistent or recurrent, surgical excision of the pericardium may be required (Beaudry, Nakamoto and Wolff, 1966; Siddiqui and Kerr, 1971).

The Treatment of Uraemic Osteodystrophy.
Patients with low serum calcium levels and evidence of significant osteomalacia should be treated with vitamin D in large doses. If the serum calcium level is normal or high, any further rise in calcium as the result of vitamin D therapy carries a high risk of troublesome metastatic calcification. In such
cases, subtotal parathyroidectomy should probably be carried out before vitamin D is given (Stanbury, 1967).

From first principles it would appear reasonable to avoid prolonged parathyroid stimulation by keeping the serum calcium and phosphate levels as near to normal as possible. Oral aluminium hydroxide blocks absorption of phosphate from the gut and lowers the serum phosphate level. In patients on dialysis, the use of slightly high dialysate calcium concentrations in the dialysis solution prevents hypocalcaemia (Siddiqui and Kerr, 1971).

The Treatment of Renal Anaemia.
Since erythropoietin is not available for clinical use, the only really satisfactory treatment for renal anaemia is a successful renal transplant. Even without functioning renal tissue, however, haemoglobin levels of 7–9 g/100 ml should be achieved by most patients. Levels of 4.0–6.0 g are not infrequently seen.

Adequate dialysis will correct the bleeding tendency, control haemolysis in most patients, and remove that component of the marrow depression which is toxic in origin. Meticulous care should be given to the return of the blood from the dialyzer at the end of dialysis, and oral or parenteral iron supplements should be given (Wright, Goldsmith and Hall, 1968). Folic acid supplements are also advisable; iron deficiency and folic acid deficiency play a part in the anaemia in many patients (Hampers et al., 1967). In a few cases, haemolysis persists despite adequate biochemical control. An abnormal splenic uptake of red cells can be demonstrated in some of these cases, and if this is present, splenectomy is of value (Hartley et al., 1971).

Renal anaemia should not be treated by transfusion, unless this is absolutely essential to preserve life or relieve prostration. Transfusion depresses the slight amount of marrow activity which is present in uremic patients; its benefits are very temporary. Repeated transfusions can lead to serious reactions, and can also lead to the formation of antibodies prejudicial to the success of renal transplantation. Finally blood transfusion is probably the source of most outbreaks of serum hepatitis in dialysis units. Patients with renal failure seem to have an altered immune response to hepatitis. They remain antigen positive and highly infectious for prolonged periods of time. Dialysis involves the exteriorization of large volumes of blood. If the hepatitis virus enters a haemodialysis unit, the risk of spread to other patients and to members of staff is very high. The virus is often lethal. Because of the long incubation period, precautions against spread are extremely difficult. If at all possible, the hepatitis virus should be kept out of dialysis and transplant units. This means that routine blood transfusion should not be employed in the treatment of renal anaemia (Drukker et al., 1970). Improvement in anaemia has been reported following the injection of testosterone, 250–500 mg weekly (Shaldon et al., 1971). This important finding has yet to be confirmed by other workers.

DEFINITIVE THERAPY IN END-STAGE RENAL FAILURE

General Considerations.
Approximately 50 patients per million of the population between the ages of 16 and 55 develop end-stage renal failure each year. Perhaps 40 of these are suitable for long-term dialysis or renal transplantation (Curtis, 1971).

About 500 transplant operations were performed in Europe in 1969 (Parsons, Clark and Spoek, 1970) and during that year there were about 3,500 patients on regular dialysis (Drukker et al., 1970). This indicates that even in the developed countries only about 20 per cent of potentially suitable patients in fact receive treatment. Rigorous selection of patients for haemodialysis/transplant programmes is therefore still essential.

Because of the pressure on facilities, there is a tendency to put off starting patients on dialysis until the last possible moment. This is understandable, but the results of vacillation can be disastrous. It can lead to weeks of hospitalization for many patients, during which desperate attempts are made to control complications which would not have arisen had dialysis been started early enough. Patients should be accepted or rejected for definitive long-term therapy as early in the course of their renal disease as practicable. If they are accepted, dialysis should be started while the patient is still relatively well. A serum creatinine concentration of 15 mg/100 ml is a good if approximate yardstick.

Transplantation using cadaver donors carries a higher mortality than long-term haemodialysis, and once social and ethical factors have been taken into consideration the number of patients for whom suitable living donors are available is relatively small. The quality of life following a successful renal transplant is, however, far superior to that enjoyed
by even the most well adjusted dialysis patient. It must be stressed that transplantation and long-term dialysis are not competing forms of therapy. Each may be appropriate for the same patient at different times. The definitive treatment of end-stage renal failure involves an integrated medical and surgical approach (Clunie et al., 1971).

Dialysis.
The artificial kidney was introduced by Kolff in 1943 for the treatment of acute renal failure (Kolff and Berk, 1943). The repetitive use of artificial kidney machines in the treatment of chronic renal failure was initiated seriously in the late 1950s (Scribner et al., 1960). Most early attempts failed because of the problem of obtaining repeated access to the circulation. Haemodialysis in the adult requires a blood flow of about 200 ml per minute through the kidney machine. With repeated cut-downs, the supply of vessels capable of delivering this amount of blood rapidly became exhausted.

The introduction in 1960 of an external arteriovenous shunt of teflon and silastic was a major technical breakthrough (Quinton, Dillard and Scribner, 1960). More recently, an internal arteriovenous fistula has been evolved. This leads to the development of large, superficial arterialized veins which can readily be punctured with large needles (Brescia et al., 1966).

The principle of dialysis is simple. Blood is exposed to dialysis fluid across a semipermeable membrane. Substances small enough to pass through the pores of the membrane pass from where their concentration is high to where it is low. In time, the composition of the blood with respect to its diffusible components approaches that of the dialysis fluid. By adjusting the composition of dialysis fluid and bringing a sufficient volume of this fluid into contact with a sufficient volume of blood across a semipermeable membrane of sufficient area, almost any desired alteration in body chemistry can be achieved. By making the dialysis fluid hypertonic, or by producing a hydrostatic pressure across the dialysis membrane, net ultrafiltration of salt and water can be induced. This is important, as fluid overload frequently requires correction.

The dialysis membrane need not be outside the body. The peritoneum has a large surface area, and if 1–2 litre aliquots of sterile dialysis fluid are introduced into the peritoneal cavity and then drained at approximately hourly intervals, the biochemical situation will be corrected in 36–48 hours in all but the most catabolic patients (Boen, 1960). Repeated peritoneal dialyses are demoralizing for the patient. There is a persistent risk of infection, and the development of adhesions leads in time to technical problems. Although peritoneal dialysis is a valuable technique, it has not in the past been appropriate for the long-term management of chronic renal failure. The introduction of closed circuit systems for the delivery and drainage of peritoneal dialysis fluid has, however, lessened the frequency of infection, and the place of long-term peritoneal dialysis in the definitive management of end-stage renal failure is being reassessed (Tenckhoff et al., 1969; Jones, 1971).

At the time of writing, however, the established dialysis technique for prolonged dialysis therapy is the use of the artificial kidney machine, either on the basis of twice-weekly attendance at a hospital centre (Curtis, 1971) or thrice-weekly dialysis in the home (Robinson, 1971). Home dialysis has many advantages over hospital treatment. The patients benefit psychologically from their relative independence and medically from the fact that dialysis can be more frequent. The survival of home dialysis patients is considerably better than that of patients dialyzed in hospital. A four-year survival rate of 86.2 per cent has been reported by Moorhead and others (1970).

Transplantation of the Kidney.
The best treatment for chronic renal failure is a successful renal transplant, but not all transplants are successful. The technical problems of the operation itself and of the recovery and storage of the donor organ have largely been overcome, but the problems of rejection of the graft by the recipient remain (Calne, 1967). Immunosuppressive therapy, usually with a combination of azathioprine and prednisone, controls rejection to some extent, but even with such therapy, transplant failure still occurs in a substantial proportion of cases.

The importance of there being a substantial similarity in tissue antigens between donor and recipient is illustrated by comparing the results of operations using living related donors with those in which grafts from unrelated cadavers are employed. Where living donors are meticulously matched with recipients in terms of ABO blood groups and white cell antigens, in cases where no antigenic dissimilarity can be detected, the survival at one year with good renal function is 95 per cent (Merrill and Hampers, 1971). Even in parent-to-child transplantation, where tissue matching is of necessity not perfect, over 75 per cent of recipients are still
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surviving with good renal function at the end of one year.

The results of transplantation employing cadaver grafts have steadily improved, but the one-year survival is still only 50–60 per cent (Kidney Transplant Registry, 1971). The high failure rate in the cadaver situation is due very largely to the problems of achieving histocompatibility with unrelated donors. Antigens exist which have not yet been identified. With living related donors, even if antigen detection is incomplete, there is a reasonable genetic chance that donor and recipient will prove compatible. With unrelated donors, the genetic odds are against compatibility unless all relevant antigens can be identified and carefully matched.

The results of transplantation using cadaver donors will probably never be as good as those where living relatives provide the transplanted organ, but the situation should continue to improve. Advances have been made in the techniques of removing and preserving cadaver kidneys. Once a kidney has been chilled and perfused, it will usually remain viable for a further 10 hours. This enables organs to be transported many hundreds of miles to the most suitable recipient.

Our knowledge of transplant immunology is growing. With advances in organ preservation and transportation, the populations of several countries can be linked for the purposes of organ transplantation. Once a pool of several thousand potential recipients is established and further refinements have been made in the field of tissue typing, it should be possible to achieve a very high degree of histocompatibility even in the field of cadaver transplantation.

CONCLUSION

Fifteen years ago, end-stage renal failure had a prognosis far worse than that of most forms of cancer. It was a sentence of early death, from which there was no reprieve. Today, the five-year survival of patients without useful renal function treated by dialysis is well over 50 per cent. It should not be long before similar survivals are regularly attainable in the field of cadaveric renal transplantation.

Improvements in technique will bring about still further improvements in long-term survival, but the biggest mortality, of course, consists of those patients in whom long-term therapy is not attempted, because the facilities for treating more than a fraction of suitable cases do not exist. Part of the answer lies in governments making more money available for this form of therapy, but care must be taken to ensure that such money is not simply diverted from other equally important spheres of medical endeavour.

Hope for the future lies perhaps as much in the ingenuity of the engineer and the industrialist as in purely medical advance. Dialyzers are getting smaller; the population on dialysis is getting larger. With miniaturization and mass production, costs may be cut to the point where it becomes financially possible for the majority of patients with end-stage renal failure to be treated.

REFERENCES


