Neurology and the kidney

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Abstract

Renal failure is relatively common, but except in association with spina bifida or paraplegia it is unlikely to occur as a result of disease of the CNS. Renal failure, however, commonly affects the nervous system. The effects of kidney failure on the nervous system are more pronounced when failure is acute. In addition to the important problems related to renal failure there are both acquired and genetically determined diseases which may affect the kidney and the brain. Those acquired diseases include the vasculitides, the paraproteinaemias, and various granulomatous conditions (considered in other chapters of *Neurology and Medicine*). In two of the most commonly encountered genetically determined diseases, Von Hippel-Lindau disease and polycystic kidney disease, location of pathogenic mutations will provide improved screening programmes and, possibly, allow therapeutic intervention. Uraemia may affect both the central and peripheral nervous systems. Whereas the clinical features of uraemia are well documented, the pathophysiology is less well understood and probably multifactorial. Uraemic encephalopathy, which classically fluctuates, is associated with problems in cognition and memory and may progress to delirium, convulsions, and coma. The encephalopathy may initially worsen with periods of dialysis and almost certainly relates to altered metabolic states in association with ionic changes and possibly impaired synaptic function. Renal failure may affect the peripheral nervous system, resulting in a neuropathy which shows a predilection for large diameter axons. This may be reversed by dialysis and transplantation. The myopathy seen in renal failure, often associated with bone pain and tenderness, is similar to that encountered in primary hyperparathyroidism and osteomalacia.

Dialysis itself is associated with neurological syndromes including the dysequilibrium syndrome, subdural haematoma, and Wernicke's encephalopathy. Dialysis dementia, which was prevalent during the 1970s, has reduced in frequency with the use of aluminium free dialysate. With the introduction of transplantation and

the concomitant use of powerful immunosuppressive drugs, the pattern of neurological problems encountered in renal replacement therapy has shifted. Five per cent of patients develop nerve injuries during renal transplantation, and up to 40% of patients experience neurological side effects from cyclosporine. Furthermore, CNS infections, often fungal in type, have been reported in up to 45% of transplant patients coming to postmortem. The nature of the involvement of neurologists with their nephrology colleagues is therefore evolving.

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This review concentrates on recent developments in conditions which affect both the kidney and the nervous system, the effects of uraemia on the nervous system, and the neurological complications of dialysis and renal transplantation. The kidney receives about a quarter of the cardiac output. Its major functions are to regulate volume of body fluids, solutes, and pH and to concentrate the urine above plasma. The kidney also secretes renin and erythropoietin and has 1 α -hydroxylase activity. It is vital in the control of systemic blood pressure and the excretion of water soluble drugs and their metabolites. The effects of kidney failure on the nervous system are more pronounced when the failure is acute.

Genetically determined diseases affecting both the kidney and the nervous system

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is an autosomal dominant inherited disorder characterised by a predisposition to develop various tumours, most notably CNS haemangioblastomas and renal cell carcinoma (table 1).^{1,2} The prevalence of the condition has been estimated to be between 1/35 000 and 1/40 000.³ New mutations occur in only 1%-3% of cases of VHL. Incomplete penetrance is also probably rare. Apparent "obligate carriers" are affected but asymptomatic subjects when carefully screened. The VHL tumour suppressor gene was discovered by positional cloning in 1993 and its locus is chromosome 3p25-p26.⁴ Several mutations in this gene have been detected, but in about 20% of cases of VHL the

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Table 1 Proposed classification of von Hippel-Lindau disease (VHL) from the National Cancer Institute

Type	Clinical description
I	VHL <i>without</i> pheochromocytoma: retinal and CNS haemangioblastoma, renal cancers, and pancreatic involvement
II	VHL <i>with</i> pheochromocytoma: (A) plus retinal and CNS haemangioblastomas, (B). plus retinal and CNS haemangioblastomas, renal cancers, and pancreatic involvement

This classification is based on phenotype. Type I is the most common form. Type IIA is the next most common and has a milder clinical course. Type IIB is the most unusual phenotype of VHL.

mutation has not yet been identified. The disease is a classic example of the “two hit hypothesis” for tumorigenesis, in which a second mutation of the wild type allele in a susceptible tissue, in combination with the ubiquitous germ line mutation, leads to the development of carcinoma.

Retinal angiomas (more correctly termed haemangioblastomas, as the histology is identical to the lesions found in the CNS), are found in about 60% of patients with VHL.^{1 3 5} They are typically the earliest manifestation of the disease (mean age at diagnosis 25 years, range 1–67 years). Retinal angiomas are bilateral in 50% of patients. Profound visual loss may occur via the complications of haemorrhage, retinal detachment, glaucoma, and cataract. Regular screening and aggressive treatment by laser photocoagulation are the mainstays of management.

Cerebellar haemangioblastomas occur in 50%–70% of cases of VHL, and may be asymptomatic in up to 50%.^{3 5} Mean age at diagnosis is 30 years (range 11–78 years). The hemispheres are more commonly affected than the vermis, and the lesions may be multiple (fig 1). Mast cells are found within the lining epithelium of the cysts, and may be responsible for the production of erythropoietin, which can lead to erythrocytosis. The spinal cord, notably the craniocervical junction and conus medullaris, and brainstem are the two other sites of predilection for CNS haemangioblastomas. Syringomyelia or syringobulbia may complicate these lesions.³

Regular MRI of the whole neuroaxis with gadolinium enhancement is the mainstay of monitoring for CNS haemangioblastomas.² Neurosurgery, where possible, and radiotherapy, including stereotactic radiosurgery, may be employed for identified lesions.

Renal cysts of all sizes may be present in 85% of cases of VHL.^{1 3} Renal cell carcinoma develops in between 24% and 45% of patients with VHL at a mean age of 37 years (range 16–67 years). The evolution of the cysts, and whether they represent a precursor for renal cell carcinoma or not is controversial. Renal involvement is multicentric and bilateral in over 75% of patients. The clinical presentation and the risk of metastasis is similar to that in sporadic non-familial renal cell carcinoma.¹ Screening with both CT and ultrasound modalities is essential for the diagnosis of renal involvement in VHL.³ Multiple operations to carry out nephron sparing tumour removal may be necessary, occasionally culminating in bilateral nephrectomy. Renal transplantation

Figure 1 T1 weighted gadolinium enhanced brain MRI; coronal section, through the posterior fossa showing cerebellar haemangioblastoma.

and the need for immunosuppression may then only serve to promote tumour growth elsewhere.

The location of a pathogenic mutation within the VHL gene in most families has been of great benefit in determining those who are genotypically affected, and who therefore require careful screening. In these patients, an annual array of clinical, imaging, ophthalmological, and biochemical techniques are necessary for the early detection of tumours. The mean age at death in VHL of 49 years quoted in earlier work may now be somewhat pessimistic because of improved screening and management programmes. The commonest causes of death are complications from cerebellar haemangioblastoma and metastatic renal cell carcinoma. An example of a screening protocol for VHL in affected patients and at risk relatives is shown in table 2.¹

POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease (PKD) is a genetically heterogeneous disease that may exist in both autosomal dominant and recessive forms. The second form is one of the most common hereditary cystic diseases in children, with most cases presenting in infancy.⁶ The gene has been mapped to the chromosomal 6p21-cen region.⁷ Autosomal dominant polycystic kidney disease (ADPKD) exists in at least three distinct forms: In about 86% of affected European families the affected gene (PKD1) has been localised to chromosome 16p13.3, and in the remaining 14% a second locus (PKD2) has recently been found on chromosome 4q13–q23 and a third (PKD3) is so far unlinked.^{8 9} Mutations at the PKD1 locus are associated with a more severe clinical phenotype, with higher risk

Table 2 Cambridge screening protocol for von Hippel-Lindau disease in affected patients and at risk relatives¹*Affected patient:*

- (1) Annual physical examination and urine testing
- (2) Annual direct and indirect ophthalmoscopy with fluorescein angiography or angiography
- (3) Brain MRI every 3 years to age 50 and every 5 years thereafter
- (4) Annual renal ultrasound scan, with CT scan every 3 years (more frequently if multiple renal cysts present)
- (5) Annual 24 hour urine collection for VMA* or metanephrines

At risk relative:

- (1) Annual physical examination and urine testing
- (2) Annual direct and indirect ophthalmoscopy from age 5. Annual fluorescein angiography or angiography from age 10 until age 60
- (3) Brain MRI every 3 years from age 15 to 40 years then every 5 years until age 60 years
- (4) Annual renal ultrasound scan, with abdominal CT every 3 years from age 20 to 65 years
- (5) Annual 24 hour urine collection for VMA or metanephrines

* VMA=vanillylmandelic acid.

These guidelines are for asymptomatic subjects; symptomatic patients require urgent investigation. With the advent of genetic testing, the frequency of screening of at risk relatives may be significantly reduced.

of progression to renal failure, higher incidence of hypertension, and earlier age of death than the PKD2 variant.¹⁰ PKD1 has been fully sequenced and the protein which it encodes has been called polycystin. This is a membrane glycoprotein with multiple transmembrane domains which is expressed particularly in renal epithelial cells. Its function is as yet uncertain but it may mediate cell-cell or cell-matrix interactions, or possibly act as an ion channel regulator. Interestingly, PKD1 gene expression seems highest in the brain.⁹ Even within patients with PKD1 mutations there is marked phenotypic heterogeneity, but no clear genotype-phenotype correlation has emerged so far.

The clinical presentation of adult PCKD may be at any age from the second decade. Presenting symptoms include acute loin pain or haematuria due to haemorrhage into a cyst, vague loin or abdominal discomfort due to the increasing size of the kidneys, or symptoms of uraemia.

The most frequent and feared neurological complication of PCKD is intracranial haemorrhage from a ruptured arterial aneurysm. The prevalence of intracranial aneurysm in PCKD varies from 4% to 40% in different studies.¹¹⁻¹³ The variability may in part depend on whether there is a positive family history for aneurysm and the investigational technique employed. The higher estimate is at variance with most data and the true figure is probably nearer 5% to 15%. The pathogenic association between the renal disease and intracranial aneurysm is unknown. Lozano and Leblanc, in a retrospective study, compared the clinical characteristics of ruptured intracranial aneurysm associated with PCKD in 79 patients with those from a cooperative study of sporadic aneurysms.¹⁴ Sixty eight patients had a single aneurysm, whereas in 11 there were multiple aneurysms. In patients with PCKC with subarachnoid haemorrhage from a single aneurysm there was an excess of males (72%, $p < 0.01$) and more aneurysms of the middle cerebral artery (37%, $p < 0.05$). Mean age of aneurysms associated with PCKD was younger (mean age 39.7 years), and over 77% of PCKD associated aneurysms had ruptured by the age of 50, compared with 42% for sporadic aneurysms. Aneurysms associated with PCKD occurred irrespective of whether the patient was hypertensive or not.

Much uncertainty exists regarding the type of screening programmes needed for intracranial aneurysms in patients with PCKD.¹¹ The advent of MR angiography, with a sensitivity of about 85% and specificity in the order of 90% in comparison with the potentially hazardous conventional catheter angiography has added a new non-invasive dimension to the screening equation. It would seem reasonable in patients with a high risk of intracranial aneurysms to recommend screening with MR angiography at 2 to 3 yearly intervals, although the current National Institute of Health trial of management of asymptomatic aneurysms may provide better information on which to base a future screening programme.

In a series of 900 consecutive patients with haemorrhagic stroke from Taiwan 11 patients (1.2%) had intracranial haemorrhage associated with PCKD.¹⁵ Eight had hypertensive cerebral haemorrhage and the other three had aneurysmal subarachnoid haemorrhage. Hypertension had been inadequately treated or not even recognised in the eight patients, illustrating that not all intracranial haemorrhages in PCKD are aneurysmal in origin, and that rigorous management of hypertension is also important.

Arachnoid cysts may be more prevalent in PCKD (5.2–7.5%), compared with age and sex matched controls (1%).¹¹ Single case reports have also indicated associations of PCKD with eosinophilic granuloma and moyamoya disease¹⁶ and with familial amyloidosis, sensory and motor polyneuropathy, and vitreous opacities.¹⁷ It is also associated with a higher prevalence of mitral and aortic valve incompetence, and mitral valve prolapse.¹⁸ Such abnormalities should be borne in mind in the event of a thromboembolic stroke in a patient with PCKD.

WILSON'S DISEASE

This autosomal recessive condition is due to an abnormal gene (ATP7B) on chromosome 13q14.3 which codes for a defective copper transporting ATPase. In most European countries the prevalence of Wilson's disease at birth is 12–18/million. The neurological and hepatic involvement of Wilson's disease are well known, with about 40% of patients presenting with hepatic disease (acute or chronic hepatitis, cirrhosis, or acute liver failure) and 40% with neurological problems (tremors, dystonia,

dysarthria, drooling, or gait disturbance dominate initially).¹⁹

Disturbance of renal function is assumed to occur from the toxic effects of accumulated copper. Symptoms referable to the kidneys are uncommon in Wilson's disease but haematuria and nephrolithiasis are reported. Severe dysfunction of the proximal tubules may produce a Fanconi syndrome, resulting in generalised aminoaciduria, glycosuria, salt wasting, hypercalciuria, hypophosphataemia, acidosis, hypouricaemia, and tubular proteinuria.

In patients with chronic liver disease the hepatorenal syndrome may occur. In this syndrome the urine output is low with a low urinary sodium concentration, a residual capacity to concentrate urine (tubular function is intact), and almost normal renal histology. Advanced cases may progress to acute tubular necrosis. The pathophysiology of the hepatorenal syndrome may involve reduced medullary prostaglandin H synthase activity.

The treatment of Wilson's disease with D-penicillamine may lead to an immune complex nephropathy in 5%-10% of patients.¹⁹

FABRY'S DISEASE

This is an X linked inborn error of metabolism caused by a deficiency of the enzyme α -galactosidase A (ceramide trihexosidase). This leads to the accumulation of glycosphingolipids, especially in blood vessel walls, ganglion cells, kidney, eyes, and heart. The condition becomes evident in late childhood or adolescence. The principle neurological symptoms are of recurrent lancinating or burning pain in the limbs, with acral paraesthesia. Dysautonomia and a low grade fever may also occur.

Signs of renal dysfunction may occur in late childhood, but severe renal insufficiency and hypertension do not develop until adulthood. Lipid laden cells may be found in the urine sediment. Death usually occurs in the fifth decade, due to uraemia or cerebrovascular disease. Renal transplantation has been used to treat the renal failure, but does not provide enough enzyme replacement to cure the disease.²⁰

Acquired diseases affecting both the kidney and the nervous system

Vasculitides, paraproteinaemias, and granulomatous conditions, by their nature, involve more than one organ system and several present with both renal and neurological syndromes.^{21 22} The syndromes are dealt with in other papers in the current series of *Neurology and Medicine*, and are therefore only summarised in table 3.

The effects of uraemia on the nervous system

CENTRAL MANIFESTATIONS

Uraemic encephalopathy

Uraemic encephalopathy is an organic brain syndrome which occurs in patients with untreated renal failure and in association with dialysis. The encephalopathy is usually more severe and progresses more rapidly in patients

with an acute deterioration in renal function. The clinical course is characterised by variability from day to day, or even hour to hour. Early symptoms may be subtle, and comprise fatigue, apathy, clumsiness, and impaired concentration. Tests of attention span are often impaired at this stage.²³⁻²⁷

As the encephalopathy worsens, the patient may become emotionally labile, more obviously forgetful and sluggish, make perceptual errors, and develop sleep inversion. "Frontal lobe" symptoms are manifest by impaired abstract thinking and behavioural change. Paratonia (Gegenhalten, an involuntary and variable resistance to passive movement), grasp, and palmomental reflexes provide further evidence of frontal lobe dysfunction.

In the late stages of uraemic encephalopathy the patient may be delirious, with visual hallucinations, disorientation, and agitation which evolve into torpor, preterminal coma, and convulsions. The last are usually generalised tonic-clonic in type, although focal motor seizures are also common. Meningism may be elicited in about a third of patients. Multifocal myoclonus and asterixis (a form of negative myoclonus, derived from the Greek *sterigma*, which means without support, as well as a coarse postural and kinetic tremor characterise of the later stages of the encephalopathy. Limb tone is usually increased in uraemic coma, with hyperreflexia, ankle clonus, and extensor plantar responses. The signs may be asymmetric, with frank hemiparesis occurring in up to 45% of patients. These signs may alternate sides during the course of the illness (so called "alternating hemiparesis").²⁶

Even in patients who have been treated with renal replacement therapy, sluggishness, memory impairment, and sleep disturbances are not uncommon and may lead to impaired quality of life. Neuropsychological studies have compared the effectiveness of chronic haemodialysis and continuous ambulatory peritoneal dialysis regimens on these symptoms. Patients receiving either form of replacement therapy show significant deviations from normal controls in areas of attention/response speed, learning and memory, and perceptual coding. Choice reaction time, which measures sustained attention as well as speed of decision making, may be the most useful test to determine subtle cognitive impairment in uraemia.²⁶ The method of dialysis seems to make little or no difference to the neuropsychological variables tested.

Investigation of uraemic encephalopathy

The level of azotaemia correlates poorly with the degree of neurological dysfunction. Laboratory blood tests therefore confirm that the patient has renal impairment, but do not exclude other causes for the encephalopathy, and provide little help in monitoring neurological progress.²⁶ Analysis of CSF in the uraemic patient with meningism may disclose an aseptic meningitis, with up to 250 lymphocytes and polymorphonuclear leucocytes/mm³. The CSF protein may also be increased up to 1.0 g/l.²⁷

Table 3 The renal and neurological complications of the vasculitides, paraproteinaemias, and granulomatous conditions

Disease	Pathological features	Renal	Neurological
Vasculitides:			
Primary			
Polyarteritis nodosa	Necrotising vasculitis of medium and small vessels	70% show proteinuria and granular casts progressing to renal failure. 50% have hypertension	60% have peripheral neuropathy - most commonly painful mononeuropathy. 40% have CNS involvement with encephalopathy, focal infarction, subarachnoid haemorrhage, seizures and cranial neuropathies
Churg-Strauss angiitis	Eosinophilic necrotising vasculitis of medium and small vessels, peripheral eosinophilia	Infrequent renal involvement, rarely granular casts and hypertension	Mononeuropathy multiplex in 75%. Central nervous system involvement in 15-20% manifesting as encephalopathy, subarachnoid haemorrhage, rarely chorea
Wegener's granulomatosis	Necrotising granulomatous vasculitis affecting respiratory tract and small vessels. Crescentic glomerulonephritis	Proteinuria, haematuria, red blood cell casts, culminating in renal failure	Cranial neuropathies due to local erosion by sinus granuloma. Multiple mononeuropathy and polyneuropathy, rarely focal CNS ischaemia
Secondary:			
Infections			
Toxins	Bacterial and viral eg hepatitis B associated PAN Commonly in relation to illicit drug use	Proteinuria, granular casts culminating in renal failure	Encephalopathy, focal infarction in the central nervous system, mononeuropathy
Neoplasia	Commonly lymphoid malignancy		
Connective tissue diseases:			
Rheumatoid arthritis	Polyarthritis with synovial hypertrophy. Vasculitis of small and medium sized arteries	Rarely glomerulonephritis. Possible association with amyloidosis	Sensory or sensory motor peripheral neuropathy. Rarely mononeuropathy. Rare ischaemic central nervous system damage. Cranio-vertebral junction and high cervical cord lesions in association with atlantoaxial subluxation and pannus formation
Systemic lupus erythematosus	Immune complex deposition and direct autoantibody effects	Haematuria, proteinuria, nephrotic syndrome, renal failure	Encephalopathy in 40% including neuropsychiatric and behavioural abnormalities. Seizures as presenting symptom in 5%. Cerebrovascular accidents, chorea, cranial neuropathies. Rarely distal sensory or sensory motor neuropathy and occasionally chronic inflammatory demyelinating polyneuropathy
Sjögren's disease	Commonly presence of anti-Ro and anti-La antibodies	Lymphoid infiltration, tubular disorders and failure of acidification of urine	Peripheral neuropathy. Dorsal root ganglionopathy. Autonomic neuropathy. Cranial neuropathy seen in 40%. Psychiatric disorders and focal central nervous system disturbances which may mimic multiple sclerosis
Plasma cell dyscrasias			
Multiple myeloma	Tissue infiltration with plasma cells. Direct effect of antibodies	Proteinuria (Bence-Jones), nephrotic syndrome, chronic renal failure	Nerve root and spinal cord compression. Intracranial cerebral and cranial nerve compression. Peripheral neuropathy - relatively rare, usually axonal and sensorimotor
POEMS (Osteosclerotic myeloma)	Binding of immunoglobulins to neural components. Cytokine effects	M-protein rarely discovered in urine. Proteinuria uncommon. Haemangiomas may occur in the kidney	50% of patients have predominantly motor neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIPD)
Monoclonal gammopathies of unknown significance (MGUS)	Associated with lymphoid and non-lymphoid neoplasia and other autoimmune conditions. Probably affects 3% of the population	Rarely significant abnormality. Occasionally proteinuria and rarely amyloid deposition	Progressive sensory > motor demyelinating neuropathy (IgM), CIPD
Waldenström's macroglobulinaemia	Uncontrolled proliferation of lymphocytes and plasma cells	Proteinuria, nephrotic syndrome and renal failure	Slowly progressive sensory and motor neuropathy. Encephalopathy due to hyperviscosity syndrome. Myelopathy, cerebrovascular accidents and subarachnoid haemorrhage
Cryoglobulinaemia			
Type 1 (single monoclonal protein)	Waldenström's macroglobulinaemia, multiple myeloma, lymphoproliferative disease	See above	See above
Type 2 (monoclonal IgM rheumatoid factor and polyclonal IgG)	Chronic infections.	Renal failure (glomerulonephritis), nephrotic syndrome	Multiple mononeuropathy, sensory and motor neuropathy in 7%. Transient ischaemic attacks, cerebral infarction
Type 3 (polyclonal IgM rheumatoid factor and polyclonal IgG)	Chronic inflammatory or infective processes. Mixed essential cryoglobulinaemia		

Cerebral imaging with CT or MRI is usually unhelpful, although it will exclude other causes of confusion, such as subdural haematoma or hydrocephalus. Chronic renal impairment may be associated with cerebral atrophy. Reversible signal changes (low signal intensity on T1 weighted and high signal on T2 weighted images) in the basal ganglia, periventricular white matter, and internal capsule have been

described on MRI in chronic uraemic encephalopathy; the lesions disappear after dialysis.²⁸ They are of uncertain relevance and have not been widely reported.

The EEG is usually most abnormal in the acute encephalopathic state, within 48 hours of the onset of renal failure. There is a generalised slowing of the EEG, most marked frontally, with an excess of delta and theta waves. In

chronic renal failure the changes are less dramatic. As the uraemic state progresses, the EEG becomes slower, with a reasonable correlation between the percentage of frequencies below 7 Hz and the increase in serum creatinine.²⁴ Bilateral spike and wave complexes, in the absence of evident clinical seizure activity, have been reported in up to 14% of patients with chronic renal failure.

Pathophysiology of uraemic encephalopathy

The pathophysiology of uraemic encephalopathy is uncertain. Changes found in the brain of patients dying with chronic renal impairment are often mild, non-specific, and relate more to concomitant illnesses.²⁴ The calcium content of the cerebral cortex is almost twice that of the normal value. This increase may be mediated by parathyroid hormone activity, an effect probably independent of cyclic AMP. In dogs with experimentally induced acute or chronic renal failure, both EEG and brain calcium abnormalities may be prevented by parathyroidectomy.²⁹ In humans with renal failure, both EEG and psychological abnormalities may be improved after parathyroidectomy.³⁰

In renal impairment, the metabolic rate of the brain is reduced and this is, in turn, associated with a decrease in cerebral oxygen consumption. These changes occur despite normal concentrations of high energy phosphates. One possible explanation for these changes would be a reduction in neurotransmission, leading to a reduction in metabolic activity. Synaptosomal preparations include vesicles derived from presynaptic terminals and allow the activities of the sodium/calcium exchanger and calcium ATPase pumps to be studied. These two pumps export calcium from excitable cells and are important in maintaining the calcium gradient of 10 000:1 (outside–inside cells) which normally exists. In the presence of uraemia, there is a PTH dependent enhancement of calcium transport by both transporter mechanisms. Some studies have suggested that the ouabain sensitive sodium/potassium ATPase pump activity is decreased in both acute and chronic uraemic states.²⁴ As this pump is ultimately important in the release of neurotransmitters such as the biogenic amines, this could help to explain impaired synaptic function and reduction in the concentration of neurotransmitters which have been found in uraemic rats.

Further evidence of impaired synaptic function in uraemia comes from studies of the inhibitory effects of guanidino compounds, especially guanidinosuccinic acid, on the release of γ -aminobutyric acid (GABA) and glycine in animal models. These toxins, which are raised in brain and CSF in renal failure, probably impair the release of neurotransmitters by blocking neuronal membrane chloride channels. In addition, methylguanidine has been shown to inhibit sodium/potassium ATPase pump activity.

Finally, the role of aluminium in chronic uraemic encephalopathy is still uncertain. The source of the metal is likely to be from diet and

phosphate binding drugs.³¹ Transport of aluminium into the brain almost certainly occurs via transferrin receptors on the luminal surface of brain capillary endothelial cells. Once in the brain the aluminium may affect the expression or processing of the β A4 precursor protein which, via a complex cascade of events, may lead to extracellular deposition of amyloidogenic β A4 protein in senile plaques. It is unlikely, however, that the pathology so induced merely represents an Alzheimer-like change, as neurofibrillary tangles, which characterise Alzheimer's disease, are not commonly found in the cerebral cortex of patients undergoing renal dialysis.³²

To summarise, the pathophysiology of uraemic encephalopathy is a complex and probably multifactorial process. Initial problems reflect a functional, primarily neurotransmission defect. Subsequent dysfunction may be due to increasingly evident histopathological change, and aluminium could be of key importance in this process.

PERIPHERAL MANIFESTATIONS

Uraemic neuropathy

This complication was probably first reported in 1863 by Kussmaul (cited in Jennekens³³). Neuropathy occurs in up to 70% of patients who require therapy for chronic renal failure although, inexplicably, it is uncommon in children. The condition has an unexplained male predominance, and has a varied course, both in progression and severity.³⁴ The classic uraemic neuropathy is distal, sensory, and motor, and predominantly axonal. Burning sensations in the feet, or band-like sensations may be early sensory features, whereas weakness of foot dorsiflexion is usually the first motor complaint. Loss of the ankle jerk and impaired vibration sense in the feet are frequent early signs of uraemic neuropathy.³⁴ As the condition advances, wasting, weakness, and ascending sensory disturbance become more pronounced. Although usually sensory and motor in type, cases of either pure sensory or pure motor uraemic neuropathy have been reported.

Isolated mononeuropathies, particularly carpal tunnel syndrome, are also common in the uraemic state. These may be due to vascular steal syndromes from forearm access shunts in some cases. However, these neuropathies also occur in the non-haemodialysed patient and presumably reflect an increased susceptibility to pressure palsies, due to a subclinical neuropathy.³⁴

The vestibulocochlear nerve is the most commonly affected cranial nerve in uraemia.²⁴ Variable hearing loss and occasionally complete deafness are reported, which may reverse with dialysis or renal transplantation. Uraemia related hearing deficits must be distinguished from the ototoxic effects of aminoglycoside antibiotics and other drugs, as well as conditions associated with hereditary hearing loss and nephropathy.

Investigation of uraemic neuropathy

Although serum creatinine and urea concentrations generally correlate poorly with the

degree of clinical involvement, if the degree of neuropathy is markedly out of proportion to the level of renal impairment, this should lead to a search for coexisting causes of neuropathy. Despite the pathology of uraemic neuropathy (see below), a slowing of proximal nerve conduction is the earliest neurophysiological finding, and may occur in the absence of a clinically evident neuropathy.³³ Subsequently, as axonal loss and secondary demyelination occur, there is a decline in both conduction velocity and nerve action potential amplitude, which generally parallel the degree of clinical and pathological impairment. The CSF is rarely abnormal in uraemic neuropathy, unless there is concomitant encephalopathy (see above).

Pathophysiology of uraemic neuropathy

The condition has a predilection for large diameter axons, with relative sparing of the unmyelinated and small myelinated afferent neurons. There is a marked loss of axons and fibre breakdown in the distal nerve trunks of the legs with less severe changes proximally, normal spinal roots, and degeneration in the cervical portion of the dorsal columns. Anterior horn cells are intact but may show chromatolytic changes. Paranodal demyelination and separation of the myelin sheath from the axolemma are also found, but are considered to be secondary to the primary axonal damage.³³

Uraemic peripheral neuropathy does not develop if the glomerular filtration rate remains above about 12 ml/min, whereas the neuropathy is reversed, at least partially, by dialysis and dramatically by renal transplantation. The so called "middle molecule hypothesis", with accumulation of one (or several) neurotoxic molecules of molecular weight 300–2000 Da which are slowly dialysable has been a popular explanation for the genesis of uraemic neuropathy. No one substance has yet been convincingly shown to have a close correlation among plasma and tissue concentrations and the severity of the polyneuropathy. Candidate compounds considered include guanidino compounds, polyamines, phenol derivatives, myoinositol, and parathyroid hormone. Enzyme inhibition by toxins has also been studied, particularly the enzymes transketolase, pyridoxal phosphate kinase, and sodium-potassium ATP-ase. The aetiopathogenesis of the neuropathy may be multifactorial, explaining the apparent lack of correlation with any one variable.^{27 35}

Treatment of uraemic neuropathy

Mild neuropathies may clinically resolve completely after dialysis is started, although impaired nerve conduction usually persists on neurophysiological testing. Severe cases slowly improve but do not fully recover, even after several years of dialysis. A few patients have been reported to have a paradoxical worsening of their neuropathy on commencing dialysis. Haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) are both effective in preventing the progression of neuropathy,

but CAPD may be the treatment of choice for patients with diabetes mellitus and end stage renal failure.³³

Successful renal transplantation leads to a resolution of all but the most severe cases of neuropathy. Rapid recovery occurs in the first 3 months, followed by a slower phase over 9 months to 1 year. Sensory symptoms and signs disappear within days to weeks in many cases. Wasting and weakness are next to improve, with deep tendon reflexes recovering last of all. Uraemia related autonomic dysfunction and deafness are largely reversible within 2 years of transplantation.²⁷

Myopathic disturbance in the uraemic state

The clinical presentation of the myopathy associated with chronic renal failure is similar to that of primary hyperparathyroidism and osteomalacia. Proximal limb weakness and wasting occur, with bone pain and tenderness adding to the functional incapacity. In the absence of a peripheral neuropathy, the knee jerks are preserved or even brisk.

Serum creatine kinase concentrations are usually normal, and neurophysiological studies show a myopathic pattern without positive sharp waves or fibrillations. Muscle biopsy yields non-specific findings, with type 2 ("fast twitch") fibre atrophy.³⁶

The myopathy associated with chronic renal failure results from a complex interaction of metabolic factors, including reduced levels of 1, 25-dihydroxycholecalciferol, hypocalcaemia, hyperphosphataemia, and hyperparathyroidism. Parathyroid hormone enhances muscle proteolysis and impairs energy production, transfer, and utilisation. Vitamin D has been shown to influence muscle contractility in rodents, possibly via the calcium binding component of the troponin complex. The vitamin also accelerates protein synthesis and increases muscle ATP concentration. Some patients, but not all, with chronic renal impairment and myopathy respond to large doses of vitamin D.

Gangrenous calcification is a rare, but sometimes fatal, complication of chronic renal failure. In this condition there is ischaemia of skin and muscle due to a widespread deposition of calcium in the media and external elastic lamina of the arterial wall. A painful myopathy may ensue, with muscle necrosis and myoglobinuria.³⁶

Neurological complications associated with dialysis

DIALYSIS DYSEQUILIBRIUM SYNDROME

Dialysis dysequilibrium syndrome (DDS) was first recognised in the 1960s when patients with severe uraemia were often rapidly dialysed over short periods of time. It may occur during or after peritoneal dialysis or haemodialysis. Children and elderly people have a higher risk of developing DDS than other age groups. In its mildest form DDS may comprise restlessness, muscle cramps, nausea, and severe headache. Patients with a history of migrainous type headaches may experience identical headaches during dialysis. Symptoms generally occur towards the end of dialysis and subside over

several hours.^{24 27} A more severe form of DDS is characterised by myoclonus and delirium which can persist for several days. The disease may also produce generalised seizures, papilloedema, raised intraocular pressure, and cardiac arrhythmias. Such features are now extremely uncommon, with most deaths from DDS being reported before 1970. Today, if a patient undergoing dialysis were to become obtunded or comatose, DDS would be a diagnosis of exclusion, with other disorders, including intracranial bleeding and infection, being sought first.²⁴

Dialysis dysequilibrium syndrome arises because of an osmotic gradient which develops between the plasma and brain during rapid dialysis.²⁷ Arieff *et al* showed in uraemic dog model of dysequilibrium that an intracellular acidosis occurs in the brain in association with an increase in unmeasured organic acids. This generates an osmotic gradient and leads to a shift of water into the brain parenchyma, producing encephalopathy, raised intracranial pressure, and cerebral oedema.³⁷

Prevention of DDS is largely achieved by "slow" dialysis—that is, low blood flow rates, at frequent intervals (every 1 to 2 days). A further measure includes the addition of an osmotically active solute (for example, urea, glycerol, mannitol, or sodium) to the dialysate.

WERNICKE'S ENCEPHALOPATHY

Although thiamine is a water soluble vitamin, and might therefore be expected to cross the dialysis membrane with ease, there have been only a few reports of Wernicke's encephalopathy in patients undergoing chronic dialysis.^{27 35 38} In fact, the vitamin is not removed by dialysis to any greater degree than that which is normally excreted in urine. This may be due to the tight plasma protein binding of thiamine. The deficiency state probably only becomes manifest in special circumstances, such as a genetic predisposition, chronic malnourished patients with marked anorexia, and the use of glucose containing intravenous fluids. It also should be noted, however, that Wernicke's encephalopathy may not present in the classic way in chronic dialysis patients. Ophthalmoplegia was recorded in only one of five pathologically established cases in one series. Other diagnoses were considered in all five cases before death, including dialysis dementia, brainstem stroke, and uraemic encephalopathy.³⁸ The disorder may therefore be underdiagnosed in patients undergoing dialysis.

SUBDURAL HAEMATOMA

Subdural haematomas have been reported in 1.0 to 3.3% of patients undergoing haemodialysis and all age ranges may be affected. Contributory factors are coagulation problems associated with the uraemic state, and the use of anticoagulants for dialysis.^{35 39} There is often no preceding history of trauma.

The clinical manifestations are protean and a high index of suspicion is necessary. The patient may be generally obtunded, cognitively impaired, and ataxic, with marked day to day

fluctuations, or may display focal signs such as hemiparesis. Up to 20% of subdural haematomas are bilateral and may cause gait ignition failure and locomotor failure.

DIALYSIS DEMENTIA

Dialysis dementia (also known as dialysis encephalopathy, progressive myoclonic dialysis encephalopathy, and haemodialysis encephalopathy) was first clearly documented by Alfrey *et al* in 1972.^{40 41} The disorder is progressive, and invariably fatal unless treated. Dialysis dementia may be part of a multisystem disorder which includes vitamin D resistant osteomalacia, proximal myopathy, and non-iron deficient, microcytic, hypochromic anaemia.

In Europe, between 1976 and 1977, the prevalence of dialysis dementia was 600 per 100 000 dialysis patients, although there was a wide variation between centres (see below). The mean age of those affected in a large series was 50 years, with an age range of 21 to 68.⁴² Mean onset of symptoms after haemodialysis had commenced was 35 months in the same series (range 0.5–112 months). Death occurred 6 to 9 months after the onset of symptoms in most untreated cases. The current prevalence of dialysis dementia has been estimated at around 0.6% to 1.0% of dialysis patients.

A mixed dysarthria and dysphasia with dysgraphia has been reported as one of the earliest signs of dialysis dementia in up to 95% of cases. The patient may initially have a stuttering, hesitant speech which only occurs during and immediately after dialysis. Initially the patient may also be more apathetic and become depressed. As the disorder progresses, language function becomes more severely and persistently involved. Myoclonic jerks occur in up to 80% of cases and patients may become both ataxic and dyspraxic.^{24 27}

Convulsions develop in up to 60% in the later stages, and psychosis with hallucinations and paranoid delusions may be prominent. Frank dementia is obvious in over 95% of patients. Preterminally, the patient becomes immobile and mute.⁴³

Investigation of dialysis dementia

Abnormalities in EEG may precede clinically overt symptoms by up to 6 months. Intermittent bursts of high voltage slowing and spike and wave activity are noted, particularly in the frontal leads.⁴⁴ The EEG may show an initial deterioration after treatment with desferrioxamine has commenced (see below).

Neuroimaging studies and analysis of CSF are of no positive help in making the diagnosis of dialysis dementia but are of use in excluding other diagnoses if the clinical picture is atypical. The role of serum aluminium concentrations and the desferrioxamine infusion test are discussed briefly below.

Pathophysiology of dialysis dementia

An early finding was the marked geographical variation in the incidence of the dementia, suggesting the involvement of an environmental

toxin. High concentrations of tin and decreased rubidium concentrations in the brains of patients with dialysis dementia were noted first. Subsequent work confirmed an 11-fold increased concentration of aluminium in the cerebral cortex of patients with dialysis dementia, compared with a threefold increase of non-demented dialysed patients. These findings were rapidly linked to the aluminium concentration in the dialysate water supply.^{27 42} The European Dialysis and Transplant Association determined that 92% of cases of dialysis dementia were linked with untreated or "soft" water, compared with only 6% of cases who had received deionised water. It is now recognised that reducing concentrations of aluminium in water to below 20 µg/l by reverse osmosis seems to prevent the onset of the disease in patients who have just started dialysis. Sporadic cases of dementia still occur, however, and may relate in part to the use of phosphate binding gels such as aluminium hydroxide. Even absorption of mg via oral ingestion of these aluminium containing agents can lead to considerable accumulation of aluminium. However, as the use of these binders is so widespread, other, as yet unrecognised, factors must be involved, given the rarity of sporadic cases.^{24 27}

How aluminium interferes with neuronal function to cause the dementia, and why the transition between reversible and irreversible brain dysfunction occurs, is still unknown. Potential mechanisms include complexing with high energy phosphates, impaired enzymatic function, deoxyribonucleic acid binding, impaired hydrolysis of phosphoinositides, impaired microtubular function, reduced calmodulin activity via binding and reduced neurotransmitter uptake. Several of these mechanisms have only been demonstrated in *in vitro* models, and they are probably not mutually exclusive.

Neurofibrillary material has been found in cortical neurons of patients dying from dialysis dementia. There are, however, considerable differences both in the composition of the tangle material and its distribution compared with Alzheimer's disease.

Concentrations of aluminium in CSF are of no help in making the diagnosis of dialysis dementia.²⁷ Serum aluminium concentrations are of only limited assistance: Dialysis dementia has been reported in patients with serum concentrations ranging from 15 to in excess of 1000 µg/l (normal range <15 µg/l). Although the dementia is uncommon with serum concentrations <50 µg/l, such concentrations by no means exclude the diagnosis.²⁷

Desferrioxamine is a chelating agent which binds aluminium with greater affinity than that of the plasma proteins to which the metal is usually bound. The resulting desferrioxamine-aluminium complex is removed by dialysis. The aluminium mobilised by desferrioxamine is an index of total body aluminium. The usual desferrioxamine chelation test protocol is to infuse 40 mg/kg of the drug over the last 30 minutes of a dialysis session. The change in serum aluminium concentration is measured

between a baseline value and one taken 48 hours after dialysis. Increments varying between 100 and 200 µg/l have been described as the criterion for a positive test. The desferrioxamine chelation test has been used as an additional diagnostic test for dialysis dementia, but probably confers no advantage over and above baseline serum aluminium concentrations.

Treatment of dialysis dementia

The use of aluminium free dialysate may arrest, or even improve, the established case, but as aluminium is so avidly bound to plasma protein, very little is actually removed at subsequent dialyses. Desferrioxamine infusions are the mainstay of treatment of dialysis dementia, improving up to 70% of patients, sometimes to normal. Desferrioxamine binds aluminium with greater avidity than plasma protein and tissue binding sites. The chelated complex has a molecular weight of 600 and so is removed by dialysis. The clinical improvement is slow and therapy may need to be given once weekly for over a year.²⁷ There is a similarity to chelation treatments used for other neurological illness (for example, D-penicillamine therapy for Wilson's disease) in that there may be a period of paradoxical clinical and EEG worsening after treatment is commenced. The mechanism for this is uncertain but the deterioration may be profound, and occasionally fatal.

Neurological complications associated with renal transplantation

More than 10 000 renal transplants are now carried out worldwide each year, with an 85% to 95% 1 year graft survival. About 30% of transplant recipients will develop neurological complications, although this figure may be higher if minor drug related side effects are also included.⁴⁵ Some of these are considered below.

COMPLICATIONS RELATED TO THE TRANSPLANT PROCEDURE

Around 5% of patients acquire peripheral nerve injuries during the transplant procedure, usually because of intraoperative compression by retractors. The femoral nerve and lateral cutaneous nerve of the thigh are most commonly affected. The injury is usually neuropraxic in type and prognosis for recovery is generally good.⁴⁶

In some patients the caudal spinal cord is supplied by branches of the internal iliac arteries instead of the intercostal arteries. When the iliac artery is then used to supply blood to the allograft in these patients, spinal cord ischaemia may result. This most commonly produces a conus medullaris syndrome, with lower extremity pain and sensory abnormalities, sphincter disturbance, and mixed upper and lower motor neuron signs.⁴⁶

DIRECT NEUROLOGICAL SIDE EFFECTS OF IMMUNOSUPPRESSIVE AGENTS

Side effects relating to immunosuppressive therapy, especially cyclosporine, are some of the most common neurological problems encountered in the transplant recipient. Many

Table 4 Neurological side effects associated with immunosuppressive agents

Drug	Complications*
Cyclosporine†	Tremor (40%), encephalopathy (5%), seizures (2-6%), hemiparesis, paraparesis, tetraparesis, predominantly sensory neuropathy
Corticosteroids	Proximal myopathy, anxiety and dysthymia, psychosis (3%), "steroid pseudorheumatism", and headache, fever, lethargy on withdrawal
OKT3 monoclonal antibody	Transient influenza-like symptoms <24 hours‡ (>90%), aseptic meningitis 24-72 hours‡ (2-14%), encephalopathy 1-4 days‡ (1-10%)

* Figures in parentheses are the approximate frequencies of the complications, if known.

†FK506 (tacrolimus) produces a similar range of neurological complications to cyclosporine, but less commonly.

‡Time after starting OKT3 treatment.

are relatively minor, but others are more serious and should be recognised because they are reversible on reduction or cessation of treatment. Table 4 summarises the neurological complications caused by the immunosuppressive agents in common use.

Some 15% to 40% of patients receiving cyclosporine experience neurological side effects.⁴⁵ Higher blood concentrations of cyclosporine are associated with an increased risk of complications, although the correlation is not a close one, and metabolites which are not assayed may also be important. Factors which may predispose towards cyclosporine neurotoxicity are previous cranial irradiation, hypocholesterolaemia, hypomagnesaemia, β -lactam antibiotic therapy, aluminium overload, high dose steroids, hypertension, and uraemia.

More recently, a reversible posterior leukoencephalopathy syndrome has been described in a heterogeneous group of patients, including those undergoing renal, liver, and bone marrow transplantation and immunosuppressive treatment with either tacrolimus (FK506) or cyclosporine.⁴⁷ Abrupt increases in blood pressure are probably central in the pathophysiology of the condition, which presents with headaches, vomiting, confusion, seizures, cortical blindness, and other visual abnormalities. Brain MRI confirms extensive bilateral white matter abnormalities suggestive of oedema in the posterior regions of the cerebral hemispheres. Providing the syndrome is recognised, and appropriate antihypertensive treatment is instituted in combination with a reduction or withdrawal of the immunosuppressive agent, the outcome is excellent. Others have criticised the term "reversible posterior leukoencephalopathy syndrome", and have pointed out that the condition is clinically and radiographically similar to the previously well characterised disorders of hypertensive encephalopathy and cyclosporin induced neurotoxicity.⁴⁸

REJECTION ENCEPHALOPATHY

This may be more common in young recipients of transplants. Over 80% of cases occur within 3 months of transplantation but cases have been reported up to 2 years after surgery. The syndrome most commonly presents with convulsions, confusion, and headache, combined with systemic features of graft rejection. The EEG, neuroimaging, and CSF findings are non-specific. The release of cytokines in the rejection process may be important in the pathophysiology of this condition. Symptomatic treatment of the seizures is usually

Figure 2 T2 weighted brain MRI, axial section, showing a case of primary lymphoma with predilection for the periventricular region.

necessary, but the prognosis overall is good for complete recovery.⁴⁵

CENTRAL NERVOUS SYSTEM INFECTIONS

Renal transplant recipients are predisposed towards developing CNS infection primarily because of drug induced suppression of cell mediated immunity. Other predisposing factors include uraemia, hyperglycaemia, and indwelling catheters. Infections of the CNS, often fungal in type, have been reported in up to 45% of transplant patients coming to postmortem.^{35 45}

The timing of the infection after transplantation may give a clue to the nature of the likely pathogens. Broadly speaking, three phases exist.⁴⁵ In the first of these, the first month after transplantation, CNS infection is actually very uncommon. When it does occur, infection is usually either acquired from the donor kidney, is related to the surgical procedure itself, or was present before transplantation. Pathogens are typically those found in the general, non-immunosuppressed population.

The second phase extends from 1 to 6 months after transplantation. A combination of immunosuppressive drugs and the immunomodulating effect of common viruses means that immunosuppression is at its peak and the risk of CNS infection is greatest. Viruses (especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV)) and opportunistic organisms (especially *Aspergillus fumigatus*, *Nocardia asteroides*, and *Listeria monocytogenes*) predominate.

The third phase of risk extends beyond 6 months after transplantation has occurred. Infections at this stage are either due to the lingering effects of previously acquired infections (such as CMV retinitis, for example), opportunistic infections in those patients who have

often received higher than average immunosuppressive regimens because of chronic rejection (*Nocardia asteroides*, *Cryptococcus neoformans*, and *Listeria monocytogenes* are the most common organisms), or due to the return of a pattern of infection seen in non-immunosuppressed subjects.⁴⁵

Infections of the CNS in patients who have received a renal transplant may be difficult to diagnose, primarily due to an attenuation of the normal inflammatory response to infection. A high index of suspicion is therefore needed. In cryptococcal meningitis, for example, headache may precede the presence of obvious signs by days or weeks. Visual loss may be a relatively early feature due to optic nerve involvement and frank neck stiffness occurs late in the clinical course in many patients. Neuroimaging, followed by lumbar puncture (assuming no intracranial mass effect), is obligatory. The CSF analysis should include viral titres, fungal studies, and acid fast stain, as well as culture for *Mycobacterium tuberculosis*. Other tests, including polymerase chain reaction assays for JC virus (associated with progressive multifocal leucoencephalopathy) and fragments of *Mycobacterial* DNA, may add to the diagnostic yield from lumbar puncture, but despite this, it is often not possible to make a definitive diagnosis in reasonable time, so empirical therapy must be started. Expert microbiological advice in these situations is vital, to ensure that the range of likely pathogens is covered with drugs that penetrate adequately into the CNS.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Post-transplant lymphoproliferative disorder (PTLD) defines the range of abnormal proliferations of B lymphocytes which occur in renal transplant recipients. The range of disease, from benign diffuse polyclonal lymphoid hyperplasia to highly malignant monoclonal B cell lymphoma, is thought to be closely linked to EBV infection of B lymphocytes, and associated EBV driven lymphocyte proliferation.⁴⁵

Primary CNS lymphoma is 35-fold more frequent in recipients of renal transplants than in normal subjects, and may develop as early as 3 months post-operatively.²⁷ One third of lymphomas are multicentric and up to 40% involve the leptomeninges.⁴⁹ They have a predilection for the periventricular or septal areas (fig 2). Brain CT or MRI may show a relatively large lesion, in comparison with the clinical status of the patient. Lesions are isodense or hypodense and enhance strongly after contrast is administered. Patients typically present with either features of raised intracranial pressure or disturbances of personality and memory. Seizures are uncommon because of the deep-seated nature of the tumours. Brain biopsy is usually necessary to confirm the diagnosis. Malignant B cell lymphoma of the CNS in immunosuppressed patients carries a grave prognosis, and often responds poorly to chemotherapy and radiotherapy.⁴⁵

Conclusion

This review illustrates how primary renal dysfunction may lead to a broad constellation of neurological symptoms and signs, and to highlight current pathophysiological views. Such a brief account cannot be comprehensive.

In addition, we have described some conditions, genetically determined and acquired, in which both the kidney and the nervous system may be affected by the disease process. Important advances have been made recently in our understanding of several of these conditions, particularly at the genetic and molecular concentrations.

The relatively recent introduction of renal replacement therapies and transplantation has led to a shift in emphasis in the type of neurological problem that may be encountered on a renal unit. The nature of the involvement of neurologists with their nephrology colleagues is likely to continue to evolve in the future as transplantation becomes more widespread, and the range of immunosuppressive agents available increases.

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