Reviews in Medicine

Nephrology, dialysis and transplantation

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Nephrology

1. Urine microscopy

Careful phase contrast microscopy of freshly prepared urine sediment is one of the simplest, cheapest and most helpful investigations in nephrology and urology, but it is often omitted or delegated to the routine microbiology laboratories.¹ It should be the first investigation in all cases of haematuria or suspected glomerular disease. The rapid identification of red cell casts or dysmorphic red cells can point the clinicians in the direction of renal biopsy and away from cystoscopy and arteriography.² Doctors investigating renal patients should have access to a centrifuge and a good quality phase contrast microscope. With phase contrast, damaged or distorted red cells can easily be recognized (dysmorphic red cells).³ The extremes of osmolality experienced with passage along the nephron may be important in producing dysmorphic cells. Dysmorphic cells may have gained entry to the urinary tract via a ruptured glomerular basement membrane in an inflamed glomerulus or through a ruptured tubular basement membrane damaged by interstitial inflammation. The injury sustained during this passage is thought more likely to account for their variable and abnormal morphology.⁴ If all the red cells are of a similar size and shape and well preserved, the haematuria is more likely to have been caused by a lesion below the nephron. Urological workup is then appropriate.

2. Acute renal failure (ARF)

Progress in this area has centred on efforts to clarify the pathogenesis of ARF and on the development of a variety of potential treatments most of which remain experimental. In the clinical setting, continuous modes of renal replacement therapy have become routinely available for the treatment of ARF in the intensive care unit. In spite of this, the mortality remains high.

Pathogenesis of ARF

Changes in renal haemodynamics are a feature of all types of ARF irrespective of precipitating insult. Recent studies have examined the role of endothelium-derived vasoactive factors in these changes.

Endothelin Endothelin is a 21-amino acid peptide. It is the most potent vasoconstrictor yet discovered, being ten times more potent than angiotensin II. It has many other properties including effects on ion transport, eicosanoid synthesis, and renin and atrial natriuretic peptide (ANP) release. The renal vasculature appears particularly susceptible to its vasoconstrictive effect. Renal vascular resistance is increased by an effect on both afferent and efferent arterioles. It also reduces the glomerular ultrafiltration coefficient by inducing mesangial cell contraction.⁵ Thus both renal blood flow and glomerular filtration rate (GFR) are compromised (Table I). Factors known to increase its production rate include hypoxia, shear stress, endotoxin, thrombin, adrenalin, neuropeptide Y, and interleukin 1. Many of these factors are thought to be important in the pathogenesis of ischaemic ARF. Endothelin may well have a pathogenic role in this setting. In support of this, circulating levels of endothelin have been found to be elevated in patients with ARF.⁶ Experimentally, monoclonal antibodies to endothelin and specific non-peptide endothelin antagonists have been found to protect against the development of post-ischaemic renal damage.^{7,8} Anti-endothelin antibodies also protected against endotoxin-induced falls in GFR³.

Endothelium-derived relaxing factor (EDRF) Vasodilatation in response to acetylcholine and bradykinin is mediated by a diffusible EDRF, which has subsequently been identified as nitric oxide. Its synthesis is catalysed by nitric oxide synthase from L-arginine, and blocked by the arginine analogue L-NMMA. There are two enzyme systems, one constitutive, and responsible for the physiological production of EDRF, and the

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Table 1 Effects of endothelin and EDRF on renal haemodynamics

	<i>Endothelin</i>	<i>EDRF</i>
Renal blood flow	Decreased	Increased
Glomerular filtration rate	Decreased	No change
Afferent resistance	Increased	Decreased
Efferent resistance	Increased	Decreased
Glomerular ultrafiltration coefficient	Decreased	?Increased

other inducible, and responsible for prolonged EDRF production in some pathological circumstances. In addition to its vasodilator effect, nitric oxide inhibits platelet adhesion and aggregation. In these two actions, nitric oxide and prostacyclin potentiate each other. EDRF also reduces the release of renin and ANP⁹. Infusion of L-NMMA produces hypertension implying a physiological role for EDRF in the maintenance of normal blood pressure.¹⁰ Endothelium-derived nitric oxide also exhibits profound effects on glomerular haemodynamics,⁷ L-NMMA inducing increased renal vascular resistance, decreased renal blood flow, with little effect on GFR (Table 1). In post-ischaemic ARF, the vascular responses to acetylcholine and bradykinin are blunted, suggesting impaired release of EDRF.¹¹ Haemoglobin and myoglobin are both potent inhibitors of EDRF,^{12,13} and this action may be important in the pathogenesis of ARF associated with haemolysis and rhabdomyolysis. On the other hand, endotoxin and cytokines can stimulate the inducible nitric oxide synthase to produce a sustained burst of EDRF, with resulting vasodilatation and resistance to vasoconstrictor agents characteristic of septic shock. Administration of L-NMMA to rats with septic shock produced improvements in blood pressure, renal function, and survival.¹⁴ There is also some limited clinical experience with the use of L-NMMA in septic shock.¹⁵

Treatment of ARF

Experimental Calcium antagonists have a number of potentially beneficial effects on the compromised kidney. These include antagonism of preglomerular vasoconstriction, reduction in cellular calcium uptake in response to cell injury, and a possible action as a free radical scavenger.¹⁶ Protective effects against the development of ARF have been demonstrated in experimental models of a number of different types of ARF including post-ischaemic¹⁷ and toxic.¹⁸ Studies have been extended into the clinical setting, in which protective effects of calcium antagonists have been dem-

onstrated in the amelioration of radiocontrast induced renal impairment¹⁹ and post-transplant ARF.^{20,21}

ANP alone, or in combination with dopamine, protects against post-ischaemic ARF.^{22,23} The effect of the drugs in combination appears no greater than the effect of ANP alone,²⁴ in spite of the prevention, by dopamine, of the hypotensive response to ANP. Loop diuretics produced long-term improvement in renal function after an ischaemic insult, perhaps by reducing the proportion of nephrons obstructed by Tamm–Horsfall protein cylinders.²⁵

Most studies of therapy in experimental ARF have concentrated on attempts to modify the haemodynamic processes involved in the initiation of the condition. Agents which stimulate regeneration of damaged tubules may also have therapeutic potential. Epidermal growth factor is one such agent. It is a potent growth promoter to renal tubular cells, and has been found to accelerate recovery in mercuric chloride-induced ARF in rats.²⁶

Clinical Therapy in ARF is firmly based on aggressive resuscitation and optimization of haemodynamic parameters, attempts to nullify or reverse the precipitating insults, the appropriate use of loop diuretics and low-dose dopamine, and the early institution of renal replacement therapy should sufficient renal function not be restored by these former measures. Continuous modes of renal replacement have become standard in this situation, especially for patients managed in intensive care units. There is very little controlled information comparing different modes of therapy, but the firm clinical impression is that continuous treatments have considerable advantages over intermittent treatments particularly with respect to the maintenance of haemodynamic stability, the degree and stability of metabolic control and the capacity to provide optimal nutrition. A recent controlled trial has reported a significant benefit of pump-driven haemofiltration (continuous venovenous haemofiltration-CVVH) over spontaneous arteriovenous haemofiltration (CAVH). Mortality in the CVVH group was less than in the CAVH group in spite of a comparable degree of control of uraemia apparently based on serum creatinine levels. Mortality was inversely related to the volume of ultrafiltrate.²⁷ It was suggested that differences in 'middle molecule' clearance resulting from the differences in ultrafiltration volume might explain the effect. However, static biochemical parameters often provide a poor assessment of the adequacy of renal replacement treatments (*vide infra*).

3. Glomerulonephritis

i. Mesangial IgA disease

Mesangial IgA disease (Berger's disease) is the commonest cause of recurrent episodes of macroscopic haematuria in young adults, a point worth emphasizing to urologists. It is also the commonest type of glomerulonephritis. Recent research has concentrated on three areas: aetiology, prognosis and therapy.

Aetiology Serum IgA1 levels are higher than IgA2 in patients with mesangial IgA disease. This implies a systemic origin of the IgA rather than mucosal.²⁸ A variety of autoantibodies of IgA class have been described. Circulating complexes of IgA and fibronectin have been demonstrated.²⁹ The fibronectin component may be responsible for mesangial deposition of IgA rather than true IgA autoimmunity to glomerular antigens. There are other possibilities. IgA autoantibody to fibronectin may be present. Fibronectin may also bind to whatever antigen binds the IgA. An attractive hypothesis is that micro-organisms or their antigens that present to mucosal surfaces are bound to fibronectin. The resulting immune response produces circulating immune complexes of microbial antigens, fibronectin and IgA. Indeed, complexes such as these made *in vitro* preferentially deposited in the mesangium of experimental animals.³⁰ IgA reacting with human endothelial cell surface antigen has been demonstrated by ELISA and Western blotting in patients with mesangial IgA disease.³¹ Whether these are true autoantibodies to endothelial cells or represent IgA binding to fibronectin, is not yet clear. IgA–fibronectin complexes appear to be useful serological markers for mesangial IgA disease and probably also for Henoch-Schönlein purpura (HSP).³² The nature of the immune response may be abnormal with low affinity IgA antibodies being produced with no evidence of increasing affinity with time.

Platelets are thought to be involved in the pathogenesis of mesangial IgA disease, as they can be seen in affected glomeruli on electron microscopy.³³ They may also be found in the urine deposit.³⁴ Evidence of platelet involvement can be deduced from the finding of elevated platelet factor 4 levels in urine.³⁵ Urinary platelet factor 4 levels may help to differentiate mesangial IgA disease from thin membrane disease, both of which cause persistent isolated microscopic haematuria. The origin of urinary platelet factor 4 is from glomerular inflammation rather than plasma filtration.

Prognosis Twenty-five to 30% of patients with mesangial IgA disease deteriorate to end-stage chronic renal failure. If prognosis could be ac-

curately gauged from initial biopsy then a policy of biopsying all patients with clinical features compatible with mesangial IgA disease may then be justified. Table II summarizes factors associated with a poor prognosis. Elevated urinary interleukin 6 (Il6) (originating from mesangial cells or invading macrophages) appears to correlate with an adverse prognosis.³⁹ C4A deficiency is associated with severe disease, perhaps by reducing solubilization of deposited complexes.⁴⁰ Low molecular weight proteinuria, probably reflecting more extensive tubulo-interstitial damage, also correlates with a poor prognosis.^{41,42}

Treatment There are no large-scale randomized, prospective trials of treatment in mesangial IgA disease showing that any form of therapy is of benefit. Table III summarizes some of the more recent trials. The correlation between proteinuria and hypertension and poor prognosis argues for the early introduction of an angiotensin converting enzyme (ACE) inhibitor. Combinations of anti-platelet agents, warfarin, steroids and cytotoxic drugs have all been tried with some claims of benefit.⁵⁰

ii. Focal necrotizing and crescentic glomerulonephritis

Excluding cases occurring as part of a multi-system disease, primary focal necrotizing and crescentic glomerulonephritis can be caused by antibodies to glomerular basement membrane (10–25%), the deposition of immune-complexes (10–30%) or be the so-called 'pauci-immune' type (50–70%) in

Table II Adverse factors in mesangial IgA disease (see Alambartine *et al.*, 1991)³⁶

Clinical

Older age at onset
Absence of macroscopic haematuria
Arterial hypertension
Nephrotic syndrome

Histological

Glomerular sclerosis (Okada *et al.*, 1992)³⁷
Tubulointerstitial scarring (Nagy *et al.*, 1987)³⁸
Vascular sclerosis
Diffuse crescents
Glomerular necrosis

Laboratory

Urinary Il6 (Dohi *et al.*, 1991)³⁹
C4A deficiency (Wyatt *et al.*, 1991)⁴⁰
HLA B35
High serum IgA
Elevated creatinine (Okada, 1992)³⁷
Heavy proteinuria (Okada, 1992)³⁷
Low molecular weight proteinuria (Nagy, 1987; Woo, 1991)^{38,41}

Table III Trials of therapy in mesangial IgA disease (see Schena (1989) for review⁴³)

Agent	Author (year)	Outcome
Steroids	Kobayashi (1987) ⁴⁴	? Helpful if nephrotic
Cyclosporin A	Lai (1987b) ⁴⁵	Transient decreased proteinuria
Eicosapentaenoic acid	Lai (1987a) ⁴⁶	
Cyclophosphamide + dipyridamole + warfarin	Bennet (1989) ⁴⁷	No benefit
Dipyridamole + warfarin	Woo (1991) ⁴¹	Stable renal function
	Lee (1989) ⁴⁸	Less proteinuria
	Chan (1987) ⁴⁹	Stable renal function
Phenytoin	Egido (1984) ⁵⁰	Less proteinuria
		No benefit

which antibodies to neutrophil cytoplasmic antigens antinuclear cytoplasmic antibody (ANCA) are frequently detected. With the exception of anti-glomerular basement membrane antibody-mediated disease, treatment with high dose steroids and cyclophosphamide, at least in the short term, appears effective. In anti-glomerular basement membrane antibody-mediated disease, immediate plasma exchange in addition to drug therapy is considered mandatory to preserve renal function. Plasma exchange as an adjunct to immunosuppressive drugs remains an option in other forms of crescentic nephritis, particularly if severe renal impairment is present.⁵¹ In one recent study plasma exchange was shown to be of benefit only in dialysis-dependent patients, other patients doing just as well with combination drug therapy.⁵²

iii. Glomerulonephritis in human immunodeficiency virus (HIV)-positive patients

Two well-characterized nephropathies have recently been described in HIV-positive patients.⁵³ Microalbuminuria may precede overt nephropathy⁵⁴ and appears to be a marker for acquired immunodeficiency syndrome (AIDS) progression being positively correlated with low CD4 counts, lymphopaenia, tumour necrosis factor alpha, and elevated beta-2-microglobulin levels.

HIV-associated nephropathy (HIVAN) The light microscopy appearances of this lesion are of focal and segmental glomerulosclerosis.⁵⁵ This is a rapidly deteriorating severe nephrotic syndrome with progression to chronic renal failure in about 4 months. Blood pressure is usually normal and oedema often minimal. It is seen typically, but not exclusively, in young, black intravenous drug abusers. It is distinct from heroin nephropathy. Nephrotic syndrome can precede AIDS by many months. On ultrasound the kidneys are echogenic and enlarged remaining so despite progression to chronic renal failure. Hyperlipidaemia is said to be less marked than in other types of nephrotic

syndrome. Histologically the lesion is similar to focal segmental glomerulosclerosis with deposits of IgM, C3 and C1q. Endothelial cells contain numerous tubulo-reticular inclusion bodies. There are numerous nuclear bodies in the interstitial cells. Microcystic dilatation of the tubules is prominent. Despite these appearances which suggest the presence of viral particles, HIV antigens and DNA have not always been demonstrated in renal tissue. Prognosis is poor with death in 12 months despite dialysis. There is no effective treatment.

IgA nephropathy The light microscopy lesion seen is a mesangial proliferative glomerulonephritis.⁵⁶ Compared with HIVAN this is a relatively benign condition characterized clinically by microscopic haematuria and moderate proteinuria. Idiopathic IgA antibody reacting with anti-HIV IgG or IgM is present in the blood.⁵⁷ Elution studies have shown the presence of HIV DNA in the kidney.

iv. Serological tests for glomerulonephritis and vasculitis

Diagnosis and monitoring The laboratory investigation of patients with glomerulonephritis/vasculitis hopes to provide a specific diagnosis and to measure disease activity so that response to therapy can be monitored. Tables IV and V summarize diagnostic tests that can support a clinical or histological diagnosis in glomerulonephritis. Some of these tests also provide clinically useful markers of disease activity. It is helpful to attempt to define which laboratory parameters best reflect disease activity in an individual patient. Anti-entactin antibodies are found in many types of primary glomerulonephritis (proliferative, crescentic, membranous, membranoproliferative, IgA nephropathy) and therefore have little diagnostic value.⁵⁹ Of most value are C-reactive protein, ANCA,⁶² antibodies to native double-strand DNA, C3 and C4 and of course creatinine clearance and 24 hour protein. The limited causes of low complement

Table IV Laboratory markers in primary glomerulonephritis

Primary glomerulonephritis (GN)		
Lesion (Caucasians)	Laboratory marker	HLA associations
Minimal change	Highly selective proteinuria	DR7, B8, B12 DQW2
Diffuse proliferative		
Post-infections		DR4
Idiopathic	Low C3 (Hebert, 1991) ⁵⁸	
Focal/mesangial proliferative	None	
Idiopathic		
Mesangial IgA	None	BW35, DQW7
Membranous	IgA–fibronectin complexes (Cederholm <i>et al.</i> , 1988) ²⁹	
Focal segmental	IgA anti-entactin Ab (Saxena, 1991) ⁵⁹	B8 + DR3
glomerulosclerosis	Urinary C5b-9 (Schulze <i>et al.</i> , 1991) ⁶⁰	?DR4, DR3 + 7
Focal necrotizing and crescentic	None	
	ANCA (Kallenberg & Tervaert 1992) ⁶¹	DQW7
	Anti-GBM Ab	B7 + DRW15(DR2) + DQW6
Membranoproliferative	Low C3 (Hebert, 1991) ⁵⁸	DR7?
	C3 Nephritic factor	B8 + DR3

Table V Diagnosis and monitoring of disease activity in the multi-system vasculitides with GN

Disease	Micro PA	SLE	HSP	SBE	WG	C-SS	Cryog
Diagnosis	pANCA	α ds DNA Ab	IgA complexes	+ ve blood culture ECHO	cANCA	pANCA CXR Eosinophilia	Cryoglobulins C4
Activity	pANCA CRP PMN count	α ds DNA Ab C3 C4 CRP		SCAT CRP C3 C4	cANCA CRP		Cryocrit C4 SCAT

α ds DNA AB = antibody to native double-strand DNA; CRP = C-reactive protein; PMN = polymorphonuclear leucocyte; SCAT = sheep red cell agglutination titre; CXR = chest X-ray; ECHO = echocardiogram; Micro PA = microscopic polyarteritis; SLE = systemic lupus erythematosus; HSP = Henoch Schönlein purpura; SBE = subacute bacterial endocarditis; WG = Wegener's granulomatosis; C-SS = Churg-Strauss syndrome; Cryog = cryoglobulinaemia; pANCA = perinuclear and nuclear anti-neutrophil cytoplasmic antibody (ANCA); cANCA = diffuse cytoplasmic staining ANCA.

levels are of diagnostic value (Table VI). Repeated urine microscopy (see above) should not be overlooked as a marker of disease activity.

Anti-neutrophil cytoplasmic antibody (ANCA) ANCA is best detected by testing serum on alcohol-fixed buffy coat polymorphs. Two patterns of staining are recognized: cANCA (diffuse cytoplasmic staining) and pANCA (perinuclear and nuclear).⁶¹ The antigens involved have been identified (Table VII). It is now known that the perinuclear and nuclear staining is an artefact caused by alcohol fixation which allows the cationic myeloperoxidase antigen to bind the anionic nuclear membrane (fixation with formalin or glutaraldehyde shows the true pattern of antigen distribution and gives a cytoplasmic pattern). False positive results may therefore be seen in patients with antinuclear antibodies and antibodies to elas-

tase or lactoferrin. Confirmation of a pANCA by ELISA with a purified antigen is necessary.^{61a}

Anti-proteinase 3 and anti-myeloperoxidase antibodies can activate primed neutrophils *in vitro*. These antibodies bind to the site on the enzyme normally occupied by the natural inhibitor of the proteinase. If polymorphonuclear leucocytes are activated by intercurrent infections then anti-proteinase antibodies could provoke a flare of the underlying disease. Proteinase 3 is highly cationic and would be expected to bind to anionic sites in the glomerulus. In pauci-immune necrotizing/crescentic glomerulonephritis a cell-mediated immune response could be responsible for the glomerulitis.

Lupus anticoagulant The kidney in systemic lupus erythematosus (SLE) may be damaged by the deposition of immune complexes (glomeruloneph-

Table VI Causes of low complement levels (Hebert *et al.*, 1991)⁵⁸

I. Immune mediated	
(A) Associated with GN	
Post-infections GN	C3
Membranoproliferative GN	C3
Subacute bacterial endocarditis	C3, C4
Lupus-like syndromes	C2 deficiency, C4 null allele
Cryoglobulinaemia	C3, C4
Systemic lupus erythematosus	C3, C4
GN associated with persistent active infections	C3, C4
(B) Not usually associated with GN	
Vasculitis	
Rheumatoid	C3, C4
Idiopathic	C3, C4
Drug-induced lupus	C3, C4
Serum sickness	C3, C4
Drug hypersensitivity	C3, C4
Chemotherapy for lymphoma/leukaemia	C3, C4
Thyroiditis	C3, C4
B-cell lymphoproliferative disorders	C4, C2
II. Non-immune mediated	
Atheroembolism	C3
Severe sepsis	C3, C4
HUS, TTP	C3
Acute pancreatitis	C3, C4
Malnutrition	C3
Jejunal ileal bypass	C3, C4
Severe liver disease	C3, C4
Burns	C3, C4
Acute myocardial infarction	C3, C4
Haemolytic crisis in malaria	C3, C4

GN = glomerulonephritis; HUS = haemolytic-uraemic syndrome; TTP = thrombotic thrombo-cytopenic purpura.

Table VII Anti-neutrophil cytoplasmic antibodies (ANCA)

	<i>cANCA</i>	<i>ANCA</i>	<i>pANCA</i>
Pattern (ethanol-fixed buffy coat)	Diffuse cytoplasmic		Perinuclear/nuclear
Antigen	Proteinase 3		Myeloperoxidase
Clinical association	Wegener's > microscopic PA Necrotizing GN Crescentic GN		Microscopic PA > Wegener's Necrotizing GN Crescentic GN Rheumatoid arthritis Drug-induced lupus Ulcerative colitis Chronic active hepatitis Myasthenia gravis Juvenile chronic polyarthritis
	αGBM Ab disease		1–8% normals
False positive	Rare in normals		ANF positive patients: αHistone Ab αElastase Ab αLactoferrin Ab

α = denotes anti; Ab = antibody; ANF = antinuclear factor; PA = polyarteritis; GN = glomerulonephritis.

ritis and vasculitis), hypertension (both accelerated phase and chronic) and by a thrombotic microangiopathy. Cell-mediated immunity also plays a role. These processes are not mutually exclusive and probably frequently coexist (Table VIII).

Lupus anticoagulant is an IgG (occasionally IgM) autoantibody to widely distributed complex anionic phospholipid antigens. *In vitro* these antibodies prolong the partial thromboplastin time but clinically are associated with widespread arterial and venous thrombosis.⁶³

A clinical syndrome (Table IX) has evolved which is associated with the lupus anticoagulant both in patients with SLE and others.⁶⁴ Two types of anti-phospholipid antibody have been described. One binds the phospholipid antigens directly and the other requires beta-2-glycoprotein-1 and is particularly associated with thrombosis.⁶⁵

The recognition of this syndrome has important implications for the treatment of lupus nephritis. Therapeutic options now include treatment of acute immune-mediated inflammation, hypertensive vascular disease and thrombotic microangiopathy. Agents useful against the latter include low-dose aspirin, possibly eicosapentaenoic acid (EPA) and suitable antihypertensives such as calcium channel blockers.

v. Treatment of nephrotic syndrome

Despite expanding knowledge about pathogenesis, therapy remains largely empirical. The three histological lesions most often associated with the nephrotic syndrome will be briefly discussed.

Minimal change nephrotic syndrome Minimal change is the commonest cause of nephrotic syn-

Table VIII Mechanisms in lupus nephropathy

Renal lesions of SLE	
Glomerular	
	Proliferation (IC ± CMI?)
	Focal necrosis (IC, HT)
	Thrombosis (TM)
	Sclerosis (end stage)
Arteriolar	
	Vasculitis ± necrosis (IC)
	Vasculitis ± fibrinoid necrosis (HT, TM)
Arterial	
	Atherosclerosis
	Arteriosclerosis (HT, TM, end stage)
Venous	
	Renal vein thrombosis (NS + TM)
Interstitial tissues	
	Acute interstitial nephritis (CMI, IC)
	Ischaemia (HT, TM)

IC = Immune complex; HT = hypertension; TM = thrombotic microangiopathy; NS = nephrotic syndrome; CMI = cell-mediated immunity.

Table IX Anti-phospholipid syndrome

Obstetric
Recurrent spontaneous abortions (placental thrombosis)
Venous thrombosis
Recurrent deep venous thrombosis
Pulmonary emboli
Pulmonary hypertension
Budd–Chiari syndrome
Arterial lesions
Peripheral gangrene
Mesenteric artery occlusion
Cardiac manifestations
Endocarditis and valvular lesions
Atrial myxoma like lesions
Multiple small coronary occlusions (pseudocardiomypathy)
Renal lesions
Glomerular thrombosis
Arteriolar and arterial thrombosis
Renal vein thrombosis
Proteinuria
Hypertension
Renal insufficiency
CNS manifestations
Migraine
Epilepsy
Chorea
Multi-infarct dementia
Retinal artery occlusion
Pseudo-multiple sclerosis
Livedo reticularis
(With cerebral thrombosis = Sneddon’s syndrome)
Thrombocytopenia

drome in children. Cyclosporin A is now an acceptable alternative to steroids for inducing a remission. It does not reduce the incidence of relapses unlike cyclophosphamide. Cyclosporin A is also of value in maintaining a remission either alone or with low-dose steroids.⁶⁶

Membranous glomerulonephritis Membranous glomerulonephritis is the commonest cause of nephrotic syndrome in adults. Treatment is probably best reserved for patients with heavy proteinuria, severe hypoalbuminaemia and impaired renal function. Children and adults with asymptomatic membranous glomerulonephritis do not warrant immunosuppressive treatment. There is no consensus about to the best and safest regime. Intravenous methylprednisolone followed by oral steroids can induce a remission and may preserve renal function.⁶⁷ Duration of therapy may be an important factor in efficacy. A cyclical regime has been developed based on monthly cycles of chlorambucil followed by a month of steroids initiated with intravenous pulse methylprednisolone. This has been shown in a controlled trial to be of benefit.⁶⁸ A regime involving 6 months

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therapy with cyclophosphamide followed by 2 years of warfarin and dipyridamole showed a reduction in proteinuria in the treatment group.⁶⁹ The use of intravenous immunoglobulin appears promising.⁷⁰

Focal segmental glomerulosclerosis (FSGS) FSGS accounts for 10% of cases of nephrotic syndrome in children and 20% in adults. Only a minority of patients enter remission with steroids.⁷¹ Cyclosporin A can induce a partial remission,⁷² but relapse on cessation of therapy is common. Vascular lesions associated with focal segmental glomerulosclerosis may be accelerated by cyclosporin A which is not suitable for long-term use in glomerulonephritis because of its nephrotoxic potential. Analogies between focal segmental glomerulosclerosis and atherosclerosis have emphasized the use of other therapies such as angiotensin converting enzyme (ACE) inhibitors and lipid lowering drugs.

Adjunctive treatments in the management of nephrotic syndrome Control of hypertension is essential and there is increasing evidence that the use of ACE inhibitors may confer additional benefits over and above other anti-hypertensive agents. ACE inhibitors by themselves can significantly reduce proteinuria in nephrotic syndrome. Care should be taken not to treat patients who are hypovolaemic. Control of hyperlipidaemia in patients with persistent proteinuria may reduce the long-term risks of atherosclerosis and preserve renal function. The observation that plasma lipoprotein-a, an independent risk factor for coronary heart disease, may be raised in patients with proteinuria, adds further impetus to the need to control the dyslipidaemia associated with this condition.⁷³ Dietary advice together with the HMG CoA reductase inhibitors represent the current best treatment approach. Chan *et al.* treated 14 patients with nephrotic syndrome with lovastatin for 6 months.⁷⁴ One patient developed rhabdomyolysis and one patient severe hypertriglyceridaemia. Total cholesterol fell by 31% and LDL cholesterol by 43%. In the group as a whole there was no change in proteinuria or glomerular filtration rate although those patients with well preserved pretreatment glomerular filtration rate showed an increase suggesting that early intervention might help preserve renal function. Lovastatin treatment for 12 weeks in diabetics also showed a marked reduction in total cholesterol and LDL cholesterol, but no effect on proteinuria or creatinine clearance.⁷⁵ Clearly much longer term larger studies are required.

vi. The use of intravenous immunoglobulin (i.v. Ig)

Intravenous immunoglobulin (i.v. Ig) was first reported to increase platelet counts in idiopathic thrombocytopenic purpura. In 1984 it was shown to be effective in Kawasaki disease⁷⁶ and is now the treatment of choice. Its use has recently been expanded to include the multi-system vasculitides⁷⁷ membranous glomerulonephritis⁷⁰ and the anti-phospholipid syndrome.⁷⁸ A multi-centre trial is currently in progress to assess the efficacy of i.v. Ig in the multi-system vasculitides.

Several theories have been advanced to explain the mechanism of action. Intravenous Ig may produce reversible blockade or down regulation of Fc receptors on the cells of the reticuloendothelial system. Alternatively it may contain anti-idiotypic antibodies that suppress autoantibody production.^{79,80}

4. Diabetic nephropathy

Diabetic nephropathy accounts for increasing numbers of patients on renal replacement programmes. The resulting vast economic and social burden has stimulated inquiry into means of retarding disease progression.

i. Predictors of progressive nephropathy

The concept that microalbuminuria (the excretion of small amounts of albumin in the albugest negative range) is an important predictor of progressive nephropathy, is now well established. Some problems of definition have been resolved. A urinary albumin excretion rate of between 20–200 µg/minute in a timed overnight sample or an albumin to creatinine ratio of 2–20 mg/mmol in an early morning specimen are commonly accepted criteria.⁸¹ Lower levels of albumin excretion may also be predictive of renal damage.⁸²

The importance of microalbuminuria as a predictor of progressive renal disease has been underlined by the clear associations which have been demonstrated with structural renal damage. Patients with microalbuminuria have increased basement membrane thickening and more mesangial expansion compared with normoalbuminuric patients.⁸³ The concept has also emerged that excretion of abnormal amounts of protein might itself cause glomerular damage and contribute to the downward spiral of renal function in diabetic and other proteinuric nephropathies.⁸⁴

Diabetics with microalbuminuria also have elevated blood pressures compared with their normoalbuminuric counterparts.⁸⁵ There is a complex relationship between these two factors and the progression of renal damage. Clearly both micro-

proteinuria and hypertension can result from renal damage inflicted by the metabolic derangements of diabetes. Both may accelerate progression of renal disease. They are not independent since hypertension aggravates microalbuminuria. Recently it has been suggested that hypertension may play a more fundamental role. Some studies have shown a higher incidence of parental hypertension in diabetics with nephropathy compared to those without, suggesting that a genetic predisposition to hypertension may be an important determinant of progression.

This notion gained support from studies demonstrating significantly increased red cell sodium–lithium countertransport (Na–Li CT), a marker for essential hypertension, in diabetics with nephropathy compared to those without.^{72,86} It was also demonstrated that this abnormality preceded the onset of clinical nephropathy and correlated with hyperfiltration,⁸⁷ itself a possible marker of impending clinical nephropathy. Recently, however, a number of studies have cast doubt on these findings, suggesting variously that the abnormality is confined to a subgroup of patients with diabetic nephropathy,⁸⁸ that it is a characteristic of the diabetic process itself,⁸⁹ and that it does not exist at all in this setting.⁹⁰ It is difficult to reconcile these diverse findings. A recent study has shown that Na–Li CT activity in red cells is dramatically higher post-prandially compared with the fasting state.⁹¹ This study confirmed that Na–Li CT activity is elevated in diabetic nephropathy, though, in the post-prandial state, a modified method using a higher external sodium concentration was required to demonstrate it.

A number of other factors have been implicated in the progression of diabetic renal disease including protein intake, hyperfiltration and lipid abnormalities. There is some evidence for the former, in that dietary protein restriction has been shown to reduce the rate of progression of established nephropathy.⁹² There is little evidence though, that the other influences mentioned above, operate as independent risk factors. There is, however, little doubt that the major forces influencing progression are microalbuminuria and hypertension.

ii. Treatment

Established nephropathy Anti-hypertensive treatment is of proven benefit in preventing the progression of established nephropathy. There is now some evidence for the concept that ACE inhibitors may confer some specific benefit, additional to those obtained by use of conventional anti-hypertensive agents. In a long-term prospective study, treatment with enalapril plus frusemide resulted in a significantly slower rate of decline of renal function in patients with insulin-dependent

diabetes than treatment with metoprolol plus frusemide, in the face of a comparable reduction in blood pressure.⁹³ A similar result was obtained when enalapril plus conventional therapy was compared with placebo plus conventional therapy in non-insulin-dependent diabetics with nephropathy.⁹⁴ In both studies the protective effect was biphasic. The initial 6 months of therapy was characterized by a more rapid fall in glomerular filtration rate in the enalapril group, with the protective effect emerging in the later periods of study. Although these data are suggestive of a specific benefit of ACE inhibitors in diabetic nephropathy, other studies have shown no such effect⁹⁵ and the results of ongoing trials are awaited.

Other avenues of treatment have been explored. There is some evidence that protein and phosphate restriction may be useful,⁹² but the benefits are probably small in relation to those obtained with anti-hypertensive therapy and may not be additive. There is little evidence that improved diabetic control reduces the rate of progression of established nephropathy. However, dramatic histological improvements were seen after transplantation of kidneys affected by diabetic nephropathy into non-diabetic recipients.⁹⁶ Successful pancreas transplantation has also been shown to be associated with less severe nephropathy in kidneys previously transplanted into diabetic patients.⁹⁷ This testifies to the vast gap in quality separating the degree of control achieved by our treatment regimes and that associated with normal glucose homeostasis.

Incipient nephropathy Improved metabolic control can retard the progression from microalbuminuria to clinical proteinuria. Conventional anti-hypertensive therapy has a similar protective effect, as do ACE inhibitors. Whether ACE inhibitors confer specific protection, in addition to that afforded by their anti-hypertensive effect, has been the subject of intense enquiry. Evidence in favour of such a specific effect is accumulating. The addition of an ACE inhibitor to conventional anti-hypertensive therapy in microalbuminuric diabetics produced a significant reduction in the urinary albumin excretion rate, with no change in glomerular filtration rate or blood pressure assessed by 24 hour ambulatory monitoring.⁹⁸ In normotensive patients, treatment with captopril also demonstrated a significant anti-proteinuric effect when compared to placebo, though blood pressure fell slightly in the captopril-treated group.⁹⁹ A meta-analysis of published studies of different anti-hypertensive agents in microalbuminuric and overtly proteinuric diabetics demonstrated that treatment with an ACE inhibitor resulted in a greater anti-proteinuric effect for a similar blood pressure fall.¹⁰⁰ Interestingly treatment with nifed-

pine produced an increase in proteinuria, a finding which is consistent with its known effects on renal haemodynamics.

5. Polycystic kidneys

Clinical features The clinical spectrum of adult autosomal dominant polycystic kidney disease (APKD) has been widened in recent years to involve other organs, perhaps indicating a common defect in connective tissue or ground substance (Table X). The most serious of these associated pathologies is the presence of intracranial aneurysms. Chapman *et al.*¹⁰³ studied 92 young subjects with APKD and found an incidence of 4%, a four-fold increase over the general population. They recommended high-resolution computed tomographic (CT) scanning as a relatively non-invasive safe screening test. Nuclear magnetic resonance angiography will probably prove superior.

Is screening for unruptured intracranial aneurysms in APKD justified? The early mortality rate of a ruptured intracranial aneurysm is in excess of 50%. Conventional angiography carries an appreciable morbidity and mortality as does surgical intervention. At present it does not seem possible to identify high-risk patients as familial clustering of aneurysms has not been confirmed. There does seem to be a marked intrafamilial variation in phenotypic expression.¹⁰⁸ Furthermore

about 25% of patients with aneurysms will have multiple aneurysms. The probability of rupture of an asymptomatic aneurysm in adult polycystic kidney disease is unknown. The size of the aneurysm (> 10 mm) is related to rupture risk. Some authors have recommended elective surgery in men under the age of 69 and women under the age of 75 with aneurysms over 10 mm in diameter.¹⁰⁹ The decision to operate will have to incorporate such factors as local expertise and the surgical accessibility of the aneurysm. In patients who have already survived aneurysm rupture, the indication for surgery is much stronger.

Screening for APKD There are at least two distinct genetic inheritances for APKD. One is on the short arm of chromosome 16 and linked to the alpha-globin gene (APKD1) and another appears to be on chromosome 2 (APKD2). The clinical presentation of APKD in those cases not linked to chromosome 16 is different with patients presenting much later in life with cysts and chronic renal failure. The limitations of pre-natal and family screening techniques for APKD have recently been reviewed.¹¹⁰ To be reliable a large kindred spanning several generations should be available for study.

Cyst growth Only one to two nephrons contribute to cyst formation. Tissue culture work suggests that cyst growth is due to an enhanced capacity of tubular epithelial cells to proliferate. Epidermal growth factor provokes an exaggerated proliferative response in culture experiments and has been found in cyst fluid. In a mouse model of recessive polycystic kidney disease, increased expression of several oncogenes has been detected.¹¹¹ Cyst growth depends on the presence of secretion by the epithelial cells which is enhanced by factors that increase cyclic AMP and is suppressed by factors that inhibit it. In human cyst tissue there appears to be altered epithelial cell polarity with the sodium/potassium ATPase pump located on the apical border of the cells and thus lining the inner wall of the cyst. It has also been shown that activation of the renin angiotensin system enhances cyst growth in an animal model.¹¹²

Extracellular matrix The simplest hypothesis that explains at least in part the renal and extra-renal manifestations of APKD is that the fundamental defect is of basement membrane or extracellular matrix structure. Early changes in the kidney include splitting and reduplication of basement membrane with more advanced abnormalities being seen in the basement membrane around cysts. A wide range of abnormalities in composition of extracellular matrix has been demonstrated but no single defect has been clearly identified.¹¹³

Table X Clinical spectrum of APKD (Gabow, 1990)¹⁰¹

<i>Adult polycystic kidney disease</i>	
Kidney	
Cysts	
Hypertension	
CRF (50% by age 73)	
Renal adenomata (Gregoire, 1987) ¹⁰²	
Brain	
Intracranial aneurysms (0–41%)	
Anomalous vessels (Chapman, 1992) ¹⁰³	
Heart	
Mitral valve prolapse (Timio, 1992) ¹⁰⁴	
Aortic regurgitation	
Gut	
Diverticulosis (Scheff, 1980) ¹⁰⁵	
Liver	
Cysts (bile ducts) ≥ 30% (Milutinovic, 1980) ¹⁰⁶	
Hepatic fibrosis in APKD (Cobben, 1990) ¹⁰⁷	
Pancreas	
Cysts	
Ovary	
Cysts	
Uterus	
Cysts	
Abdominal wall	
Hernia (Gabow, 1990) ¹⁰¹	

Treatment of APKD Hypertension develops early in some patients with APKD even before there is significant renal impairment. There appears to be activation of the renin angiotensin system early in the course of the disease.¹¹⁴ Renovascular resistance is increased and effective renal plasma flow (ERPF) reduced. Treatment with ACE inhibitors has been shown to reduce the elevated renal vascular resistance without changing the glomerular filtration rate. Filtration fraction (GFR/ERPF) fell, indicating a rise in ERPF. Mean arterial blood pressure also fell. In normal family controls ACE inhibition produced no significant changes.¹¹⁴ It was then suggested that there is inappropriate activation of the renin angiotensin system for the state of the extracellular fluid volume,¹¹⁵ and thence that ACE inhibition may have a beneficial effect on progression. Long-term trials are clearly needed. Recently there has been some renewed interest in cyst drainage. Pain can be relieved without deleterious effect on the rate of progression.¹¹⁶

Chronic renal failure

1. Atherosclerotic renal artery stenosis

Introduction

Atherosclerotic renal artery stenosis (ARAS) is underdiagnosed in life, often inadequately investigated and frequently managed inappropriately.

Incidence

The precise incidence of ARAS is unknown. It has been estimated that about 105 patients per million per year develop ARAS. Clearly the prevalence depends on the population being studied. Fourteen per cent of our patients with end-stage chronic renal failure over the age of 55, have ARAS.¹¹⁷ Where the renal arteries have been seen during coronary angiography or lower limb angiography, the incidence of ARAS has been reported at 19% and 42%, respectively.^{118,119} In non-insulin-dependent diabetics with an elevated plasma creatinine the incidence of ARAS is about 40%.¹²⁰

Clinical features

It is clear that ARAS can often be asymptomatic or overshadowed by the clinical manifestations of atheroma in other major arteries. Before diagnosing asymptomatic ARAS it is worth considering what constitutes a normal plasma creatinine. In young adults a plasma creatinine of 60 $\mu\text{mol/l}$ represents a GFR of approximately 120 ml/minute. For each doubling of plasma creatinine

there is a halving of GFR. Thus a plasma creatinine that appears only slightly elevated, for example 150 $\mu\text{mol/l}$, represents a loss of over half the total renal function. Similarly the criteria for what is considered to be an elevated blood pressure need to be revised downwards in the light of recent studies in older patients. Blood pressures in excess of 160/90 mmHg in the over 60s probably warrant investigation and treatment.^{121,122} It is just this group of patients with minimally elevated plasma creatinine and hypertension over the age of 60, in which atherosclerotic disease in general is most likely to be found.

The clinical presentations of ARAS include hypertension (often of less than 5 years duration). The hypertension may be 'newly worse' and more difficult to control. Pickering recently pointed out that hypertension with recurrent episodes of left ventricular failure is commonly associated with ARAS.¹²³ The expanding use of ACE inhibitors has revealed unsuspected cases of ARAS and in one series this condition accounted for 4% of all patients presenting with acute renal failure.¹²⁴ Frequently ARAS is part of a more generalized disease process with atheroma of the coronary and cerebral circulations as well as lower limb and sometimes mesenteric ischaemia.

In order to diagnose patients with ARAS a high degree of clinical suspicion is essential. Hypertension in an arteriopathy with a missing pulse or bruit (not necessarily a renal bruit) should alert the clinician to the possibility of underlying ARAS.

Diagnosis

The pre- and post-captopril renogram is a helpful preliminary screen.¹²⁵ A baseline renogram (DTPA or Mag III) is repeated on a subsequent day, one hour after 25 mg of oral captopril. The ischaemic kidney or kidneys elaborate angiotensin II (A II). A II constricts the efferent glomerular arteriole preserving glomerular filtration pressure despite reduced perfusion. Abolition of intrarenal A II production reduces glomerular filtration but less so renal blood flow. This is reflected in a change in the renogram which shows an increased disparity of divided renal function and a prolonged time to peak activity in the ischaemic kidney. In patients in whom the clinical probability of ARAS is very high and the baseline renogram typical, the post-captopril scan may be omitted and intra-arterial digital subtraction angiography (IA-DSA) undertaken. Intravenous DSA does not give the surgeon or radiologist enough anatomical detail on which to plan intervention. Magnetic resonance imaging (MRI) angiography may replace conventional arteriography. Even with smaller catheters and lower doses of contrast IA-DSA may produce significant morbidity both with respect to local

trauma to the punctured artery and more remote complications (emboli and contrast nephrotoxicity). Selected patients need special precautions, for example, good hydration (left ventricular function permitting) and low dose dopamine. It is sometimes necessary to dialyse patients after angiography if renal failure or cardiac decompensation occur. Clinicians should be aware of the cholesterol emboli syndrome which presents like a vasculitis (livedo reticularis, fever and acute renal failure). Hypocomplementaemia and eosinophilia are typical.¹²⁶ The syndrome may occur spontaneously or after angiography in patients with atherosclerosis.

Investigation must include an assessment of both coronary and cerebral circulations as well as a detailed assessment of the risk factors and causes of atherosclerosis. Critical coronary or cerebral lesions may need attention before the renal artery.¹²⁷

Intervention in ARAS

Can aggressive investigation and intervention in ARAS be justified? There are three main points that justify an active approach.

1. Natural history of ARAS. Serial angiogram studies have shown that ARAS is a progressive disease. Forty per cent of patients with unilateral ARAS develop contralateral disease over 4 to 5 years. Forty per cent of severe stenoses ($> 75\%$) occlude over a 2 year period.¹²⁸

2. Developments in interventional techniques.

- (a) Percutaneous transluminal angioplasty (PTA). For lesions that are more main trunk than ostial, PTA has a place. In selected patients with high surgical risk, PTA may be the only intervention available. In experienced hands and with careful patient selection this technique can be safe and effective. Recurrence of the stenosis may occur so that follow-up and repeat PTA may be required.

- (b) Renal revascularization by bypass procedures. There have been great strides made in vascular surgery over the last two decades. It is safer to bypass severe aortic/ostial lesions than to attempt a formal repair. It is worth emphasizing that ostial ARAS is really an aortic disease. A right renal artery stenosis can be bypassed using the hepatic or gastroduodenal artery (with or without a segment of graft). The splenic artery may be used for a left renal artery. Synthetic grafts can be inserted higher up the aorta and implanted beyond the renal artery narrowing. These procedures have significantly reduced the morbidity and mortality of renal artery surgery.¹²⁹

3. Preservation of renal function. The classical view of renal artery surgery was that it was carried out to cure hypertension or to render it easier to control. A more important consideration is preservation of renal function. Patients with ARAS not

unusually present clinically after one kidney has virtually ceased to function and the second kidney is now failing. Appropriate intervention can avoid such patients requiring dialysis.

Significance of renal artery lesions

The finding of a renal artery narrowing does not necessarily mean that the lesion is haemodynamically significant. A stenosis of 70–75% or greater is usually significant. A unilaterally small kidney, particularly if perfusion and uptake are delayed, also suggests a significant stenosis. A positive captopril renogram or a rise in plasma creatinine with an ACE inhibitor suggests that the stenosis is impairing perfusion and function. Renal vein renins are sometimes of value.

Surgical intervention

With the proviso that cerebral or coronary vascular surgery may be needed first, renal revascularization is of proven value both for the control of blood pressure and the preservation/salvage of renal function. Operating on kidneys less than 8 cm in length in which there is no perfusion or nephrogram, is unlikely to be successful. Retrograde filling of the renal artery on angiography is an encouraging sign indicating good collateral circulation despite an apparently totally occluded renal artery. A perioperative renal biopsy can be helpful in identifying kidneys in which the glomeruli are non-sclerosed and therefore capable of functioning. PTA and surgical revascularization should not be seen as mutually exclusive. Failure of one technique in a given patient may be followed by success of the other. There are promising early reports of the use of stents placed after PTA for ostial lesions.^{130,131}

Medical intervention

Atherosclerosis is a generalized and progressive disease. A case can be made for the intensive medical management of all patients with ARAS, whether or not intervention is undertaken. The aetiological factors for atherosclerosis are well known and the cellular and molecular basis of atherosclerosis is being delineated in ever greater detail. Evidence is accumulating that atheroma can be reversed in other vascular beds so why not in ARAS?^{132–134} The most important prerequisite for all medical therapy is that the patient should stop smoking. Perhaps the second most important factor is obsessional control of the blood pressure. Here the choice of agents may be critical with ACE inhibitors and beta blockers being contraindicated. In the over 65s is diet and control of hyperlipidaemia likely to help? Certainly patients should

be advised to diet to ideal weight and avoid sodium rich foods if hypertensive. With the arrival of safe and effective lipid-lowering agents, patients with proven ARAS should be studied in a properly designed randomized controlled trial of intensive medical therapy.

2. *Erythropoietin*

The erythropoietin (Epo) revolution was triggered by the isolation and cloning of the Epo gene^{135,136} and subsequent clinical use of recombinant human Epo to treat the anaemia of patients with chronic renal failure requiring haemodialysis.^{137,138} The last few years have seen an explosion in our understanding of the biology and clinical applications of Epo.

The human Epo gene is located on chromosome 7 where it is encoded as a single copy gene consisting of five exons separated by four introns.¹³⁹ Besides the kidney, the liver is a well-established site of Epo production. The probable site of production in the kidney is the endothelial cells of peritubular capillaries, though there is some evidence that interstitial cells and tubular cells may also be involved.¹⁴⁰ Epo secretion is stimulated by hypoxia by a mechanism which involves an oxygen sensor located near the proximal tubules. It is not known whether the oxygen-sensing cells are the cells which secrete Epo. The oxygen sensor has recently been shown to be a heme protein which triggers Epo production when in the deoxy conformation. DNA sequences both upstream and downstream of the Epo gene are required for the hypoxic response in liver and kidney.¹⁴⁰ The target cells for the action of Epo are committed erythroid progenitor cells in the bone marrow, which have specific Epo receptors.¹⁴¹

Dosage and route of administration

The initial clinical trials of Epo demonstrated dramatic improvements in the anaemia of haemodialysed patients.^{137,138} The doses and route of administration used in these initial studies were necessarily empirical and much subsequent work in this area has focused on optimizing these. Studies of the pharmacokinetics of Epo after an intravenous dose have shown that the mean half-time for clearance from the plasma is about 5–7 hours.^{142–145} The apparent volume of distribution is close to the plasma volume.^{142,146} Renal clearance accounts for less than 3% of total body clearance.¹⁴⁶ The peak concentration achieved after a subcutaneous dose is 12.5–20 times lower than that after the same intravenous dose. Absorption from the subcutaneous site is complete after about 120 hours with a bioavailability of about 30%.¹⁴⁴

It appears though that the quality of the erythropoietic response depends on the maintenance of

adequate plasma levels rather than the absolute height of the peak plasma level,¹⁴⁵ and numerous studies have demonstrated the superiority of the subcutaneous route in clinical practice.^{145,147–149} Thrice weekly subcutaneous injection is as effective as thrice weekly intravenous injection but permits a dose reduction in the range of 30–50%. Once weekly subcutaneous injection is equally effective but permits no dose reduction.¹⁵⁰

The response to therapy is dose dependent but there are great variations in response between patients.¹³⁸ Most patients require 50–200 IU/kg/week given in two or three subcutaneous doses to achieve and maintain target haemoglobin levels. Therapy requires to be individualized and based on rigorous monitoring, and a mathematical model for Epo dosing has been proposed.¹⁵¹ In spite of the growing experience in the clinical use of Epo, recent studies suggest that underdosing is endemic.^{147,152}

Many studies have demonstrated the effectiveness of Epo in continuous ambulatory peritoneal dialysis (CAPD) patients.^{153–155} The subcutaneous route has been most commonly used and has been shown to be more effective than the intraperitoneal route.^{156,157} The optimum frequency of administration is not yet known and may be subject to variation between individuals though once weekly treatment has been shown to be effective.^{158,159} There are suggestions that CAPD patients may be more responsive to Epo than haemodialysis patients perhaps because of chronic blood losses in the latter group.¹⁶⁰

There is an increasing experience with the use of Epo in predialysis patients,^{161–166} in whom the dose range and frequency for subcutaneous administration have been found to be similar to those required in dialysed patients. There were initial fears that therapy with Epo may be associated with an increase in the rate of progression of renal failure. This was based on the propensity of Epo to produce an exacerbation of hypertension and a reduction in effective renal plasma flow. These fears appear to be largely unfounded^{162–166} though careful monitoring of blood pressure is essential and the initiation of therapy with small doses has been advocated.¹⁶⁶

Patients with haemoglobinopathies and end-stage renal failure often respond to Epo but may require substantially larger doses.¹⁶⁷ Those with end-stage renal failure complicating myeloma may also respond.^{168,169}

Beneficial effects of Epo

The beneficial effects of Epo can usually be related to the improvement of anaemia. There may be other direct effects including alterations of haemostatic parameters and improvement of platelet function though even these may be related to the

rise in haematocrit.^{170–172} Many studies have shown improvements in quality of life scores.^{173–177} Regression of left ventricular hypertrophy in spite of the tendency to exacerbate hypertension has been another important finding.^{178–181} These and other effects of Epo are alluded to in Table XI.

Adverse effects of Epo

Treatment with Epo is usually very well tolerated and there are few serious adverse effects. Nevertheless a number of possible problems may arise (Table XII). Increased blood pressure is the most commonly reported of these and occurs in about one third of patients with renal failure. The risk appears maximal in the early stages of treatment when the haematocrit is increasing. Nevertheless there appears to be no clear association with the dose of Epo nor with the rate of rise of haematocrit.¹⁸² Blood volume does not change on Epo treatment¹⁸³ so is unlikely to be a hypertensive mechanism. Haemodynamic studies though, have repeatedly shown an increase in systemic vascular resistance coupled with a reduction in cardiac output during therapy with Epo.^{183–185}

Factors which may be important in the rise in the systemic vascular resistance are shown in Table XIII. The major factor appears to be a rise in the blood viscosity during Epo treatment which is largely related to the rise in haematocrit, though the fluidity of the red cells may also be disturbed.^{186,187} Another contributory factor may be loss of the vasodilatory response to hypoxia.¹⁸⁸ Other factors appear less important though alterations in sympathetic function have been described.^{189,190} If the rise in systemic vascular resistance observed during Epo therapy was accompanied by an appropriate reduction in cardiac output, no change in blood pressure would be observed. There is some evidence that cardiac output remains inappropriately high in those patients who develop hypertension,¹⁸³ perhaps due to baroreceptor dysfunction and impaired myocardial compliance.

Grand mal seizures were reported in the early

Table XII Possible adverse effects of treatment with Epo

Hypertension
Fits
Increased clotting
Flu-like syndrome
Reduced dialyser efficiency

Table XIII Factors associated with the rise in systemic vascular resistance during Epo therapy

Increased blood viscosity
Increased haematocrit
Decreased red cell fluidity
Loss of hypoxic vasodilatation
Direct vasoconstrictor effect of Epo
Activation of neurohumoral systems
Renin–angiotensin system
Sympathetic system
Imbalance of local endothelial factors
EDRF
Endothelin

clinical studies of Epo,¹³⁸ though subsequent controlled studies showed no difference in prevalence between the treated and placebo groups.¹⁹¹ Nevertheless, seizures do occur in some patients early in the course of Epo therapy at a time when haematocrit and blood pressure are increasing rapidly, and most of these patients appear to have hypertensive encephalopathy.¹⁹² Hypertensive encephalopathy is usually the result of a breakdown in cerebral autoregulation,¹⁹³ resulting in hyperperfusion, damage to the blood–brain barrier, exudation of protein, and focal cerebral oedema. Cerebral blood flow is usually reduced in response to the rising haematocrit during Epo therapy,^{194,195} but whether this adaptation is always complete remains to be established.

An increase in the number of thrombotic events has been reported during Epo therapy, though the finding is not substantiated by placebo-controlled studies.¹⁹⁶ As haematocrit increases, vascular access particularly PTFE and bovine grafts, may be at increased risk and low-dose aspirin prophylaxis has been recommended. Other haemostatic changes occur^{170–172} but there is no evidence that Epo produces a hypercoagulable state.¹⁹¹

Epo and the efficiency of dialysis

An increase in haematocrit reduces plasma water flow through the dialyser leading to a decrease in solute clearance and ultrafiltration rate. This effect on solute clearance is dependent on the diffusability of the solute across the semipermeable membrane. The clearances of easily diffusible solutes, such as

Table XI Reported beneficial effects of treatment with Epo in chronic renal failure

<i>Effect</i>
Quality of life
Exercise capacity
Cognitive function
Neuromuscular function
Sexual potency
Regression of LVH
Improved haemostasis
Improved pituitary function
Reduced cytotoxic antibody titres

urea, are less affected than those of less readily diffusible solutes. This is because the fall in plasma water flow is offset by an increased delivery of intracellular water (red cells contain 80% water), from which solutes such as urea can readily diffuse. Clearances of less readily diffusible substances, such as creatinine, and those whose intracellular concentrations are maintained by active transport processes, such as potassium and phosphate, are much more susceptible to a rising haematocrit.¹⁹⁷ The magnitude of the expected reduction in dialyser efficiency consequent on an increase in haematocrit from 20% to 33% would be expected to be of the order of 16% for poorly diffusible substances and less for those readily diffusible, since this is the proportional reduction of plasma-crit (from 80% to 67%).

A number of studies have addressed the clinical relevance of these theoretical considerations. In chronic haemodialysis employing conventional membranes, there was no change in Kt/V (urea) and protein catabolic rate (see p. 532) consequent on a mean increment in (a measure of dialysis efficiency) haematocrit from 21 to 34%. However, predialysis potassium concentrations were significantly higher, the use of phosphate binders increased (as did the heparin dose), and the dialyser efficiency for creatinine, potassium and phosphate decreased by 15%, 9% and 17%, respectively. Similar changes were seen in patients undergoing high-efficiency dialysis.¹⁹⁸ Hence it appears that only small changes to dialysis schedules, heparin dose and phosphate binder dose are required to counteract the effects of clinically relevant increments in haematocrit.

The effect of rising haematocrit on solute clearance and ultrafiltration rate in CAPD patients is less well studied. The available studies have shown no effect on either solute clearance or ultrafiltration,^{199,200} decreased solute clearances,²⁰¹ and surprisingly increased ultrafiltration.²⁰²

Resistance to Epo

Most patients with chronic renal failure respond well to Epo therapy. However, a small proportion of patients require much larger than average doses and a tiny minority do not respond at all. The common causes of poor response (termed Epo resistance) are shown in Table XIV. By far the commonest cause of poor response is iron deficiency which may predate Epo therapy (in which case the indication for Epo is suspect), or occur as a consequence of a previous good response. The diagnosis of iron deficiency is difficult in patients with chronic renal failure. Both the serum ferritin level and transferrin saturation may be misleading. The transferrin saturation and iron-binding capacity correlate better with Epo response than

Table XIV Factors associated with resistance to Epo treatment

Iron deficiency
Occult blood loss
Vitamin deficiency
Folate
B12
B6
Inflammatory states
Infection
Surgery
Secondary hyperparathyroidism
Aluminium intoxication
Haemoglobinopathies
Chronic haemolysis
Malignancy
Protein-calorie malnutrition

does serum ferritin, suggesting that the functional availability of iron in the plasma may be more important than the actual size of the body iron stores in determining response.²⁰³ Determination of the percentage of hypochromic red-cells may be a more sensitive index of iron deficiency.¹⁸¹ Almost all patients require supplementation with iron in order to maintain a response and many require iron by the intravenous route. The suggestion has been made that suboptimal doses of Epo markedly reduce serum ferritin levels.²⁰⁴

The other major cause of poor response to Epo is the presence of inflammation due to infection, surgical interventions, autoimmune disorders or malignancy.²⁰⁵ A reduction in iron availability for haem production from iron stores in the endoplasmic reticulum,^{205,206} and increased cytokine production leading to decreased Epo production or end-organ resistance to the action of Epo^{207,208} are possible explanations for this phenomenon. An interesting exception is the increased response to Epo which occurs in the context of viral hepatitis. This may be attributable to increased production of Epo by newly formed hepatocytes.²⁰⁹

3. Mineral metabolism and renal bone disease

Pathophysiology of secondary hyperparathyroidism

1,25(OH)₂D₃ directly suppresses parathyroid hormone synthesis²¹⁰ and deficiency of 1,25(OH)₂D₃ is considered to be a major stimulus to hyperparathyroidism in chronic renal failure (CRF). However, in early CRF levels of 1,25(OH)₂D₃ are normal. Recently it has emerged that 1,25(OH)₂D₃ receptor density on parathyroid cells is reduced in CRF,^{211,212} though the binding affinity of the receptor for 1,25(OH)₂D₃ is unchanged.²¹² Uraemic toxins may reduce genomic synthesis of

1,25(OH)₂D₃ receptors by inhibiting the interaction of the hormone-receptor complex with nuclear chromatin.²¹³ This reduced receptor density probably accounts for the resistance of the parathyroid glands to suppression by 1,25(OH)₂D₃ which is encountered in renal failure.²¹⁴ Administration of 1,25(OH)₂D₃ increases the number of vitamin D receptors in a dose-dependent fashion,²¹⁵ thus restoring the regulation of parathyroid hormone secretion toward normal, and increasing the sensitivity of the glands to calcium. In line with this, the elevated set point for parathyroid hormone suppression by calcium in CRF is reduced by the administration of 1,25(OH)₂D₃.^{216,217}

Skeletal resistance to the calcaemic action of parathyroid hormone may also contribute to the genesis of secondary hyperparathyroidism in CRF. Deficiency of 1,25(OH)₂D₃ and hyperphosphataemia are factors which augment this resistance.²¹⁸ Parathyroidectomy reverses the problem. In spite of this it does not seem that the resistance is due to down regulation of parathyroid hormone receptors in response to high circulating levels of parathyroid hormone.²¹⁹ Calcitonin may be involved since its absence normalizes the calcaemic response to parathyroid hormone in uraemic rats.²²⁰

Phosphate retention is also thought to play a role in the development of secondary hyperparathyroidism in CRF. The mechanisms have been thought to be either direct physicochemical interaction of phosphate with calcium leading to relative hypocalcaemia, and phosphate-induced suppression of 1,25(OH)₂D₃ synthesis. The finding that phosphorus restriction can reverse hyperparathyroidism in uraemia independently of changes in serum calcium and calcitriol levels is therefore intriguing.²²¹

Therapy of renal bone disease

Treatment and prevention of phosphate accumulation in CRF remains unsatisfactory.²²² Problems with aluminium accumulation place great restrictions on the use of aluminium-containing phosphate binders. Calcium carbonate is a useful alternative²²³ but hypercalcaemia occurs frequently.²²⁴ Calcium acetate has theoretical advantages,^{225,226} but these have proved difficult to demonstrate clinically,²²⁷ and hypercalcaemia remains a problem. Lowering of the dialysate calcium concentration has enabled larger doses of calcium-containing phosphate binders to be used, in both haemodialysed and CAPD patients, with less risk of hypercalcaemia and without compromising net calcium balance.^{228,229}

Intravenous pulse therapy with 1,25(OH)₂D₃ is effective in suppressing parathyroid hormone levels

in patients with severe secondary hyperparathyroidism.²³⁰ Pulsed therapy proved more effective than continuous treatment in suppressing parathyroid hormone levels in experimental animals,²³¹ suggesting that the parathyroid gland is more responsive to peaks than to steady-state levels. It appears though that intermittent oral treatment is as effective as intermittent intravenous treatment.²³² One of the major problems in treating secondary hyperparathyroidism is the remarkable capacity of the parathyroids to escape from control. It seems that tolerance to pulsed calcitriol may also emerge after relatively short treatment times.²³³ Other approaches have been used. Oral 24,25(OH)₂D₃ has been shown to suppress parathyroid hormone levels in dialysed patients many of whom had hypercalcaemic hyperparathyroidism.²³⁴ The synthesis of a non-calcaemic analogue of vitamin D₃ is an exciting development. This compound, 22-oxacalcitriol (OCT), has been shown to be as effective as 1,25(OH)₂D₃ in suppressing parathyroid hormone levels, but 100 times less effective in mobilizing bone calcium, and 1000 times less effective in stimulating intestinal calcium transport.²³⁵ Clearly such compounds have major clinical potential in the treatment of secondary hyperparathyroidism in chronic renal failure.

Adynamic bone disease

The spectrum of bony abnormalities associated with chronic renal failure has been increased by the description of a novel form of adynamic bone disease.²³⁶ Adynamic changes in bone were formerly thought to occur in this group of patients entirely as a result of aluminium toxicity. Now similar histological changes have been described in patients in whom there is no evidence of aluminium accumulation. This idiopathic form of the disease may account for up to 24% of cases.²³⁷ The problem may be more common in elderly patients, in diabetics, and in CAPD patients.²³⁷ The entity has also been seen in predialysis patients and the suggestion made that overtreatment with calcium supplements and active vitamin D compounds may predispose to the problem by oversuppressing parathyroid hormone levels to a degree inappropriate for the prevailing level of renal function.²³⁸ Histologically the disease is characterized by markedly reduced bone turnover, with a paucity of osteoid, bone cells and a significant reduction in active remodelling sites and tetracycline uptake.²³⁷ The clinical relevance of these histological abnormalities await firm definition. Patients with the problem do seem to have a propensity to develop hypercalcaemia, and may be at increased risk of microfracture.²³⁷

Dialysis

Adequacy

All currently available modes of renal replacement therapy, with the exception of successful renal transplantation, fall a long way short of the gold standard 'to clean blood and biological fluids to a degree comparable to normal renal function'.²³⁹ These inherent limitations of dialysis therapies dictate the need for some criteria of adequacy of therapy, difficult though they are to define.

Adequacy of haemodialysis and related techniques

'Traditional' haemodialysis treatment employed long hours ordained by the 'square metre-hour' hypothesis,²⁴⁰ the rationale of which was to provide adequate clearance of 'middle molecules'. Treatment was monitored by clinical assessment and by the measurement of predialysis blood urea and serum creatinine levels. Adequacy, at least as far as small molecular weight solute clearance was concerned, was not a critical issue.

Now, however, the question of adequacy has been brought into sharp focus by pressures, largely economic, to shorten haemodialysis times. This trend has taken place without any adjustment to the monitoring process and has resulted in significantly increased mortality in haemodialysis patients, especially in the USA.^{241,242} This implies that some of the basic requirements for adequacy have remained unfulfilled and yet have been overlooked by traditional monitoring methods.

Clinical assessment remains an important tool for monitoring adequacy, but inadequate therapy can remain undetected when guided solely by clinical parameters.^{243,244} 'Static' biochemical parameters such as predialysis urea and creatinine concentrations have also been found wanting. When protein intake is deficient, the predialysis urea may remain low in spite of inadequate dialysis, and a low predialysis urea has been found to be predictive of high mortality.²⁴⁵ Similarly it has been demonstrated that predialysis creatinine levels are inversely related to mortality.^{246,247} In the dialysis population, with relatively constant rates of creatinine removal, the major determinant of the serum creatinine level is the creatinine generation rate,²⁴⁷ a reflection of somatic protein content.²⁴⁸ This implies that, in this population, creatinine levels are an indicator of nutritional status. This notion is supported by the strong correlation between predialysis creatinine and serum albumin, which is a strong predictor of mortality in all populations.²⁴⁹

There are a number of alternative methods of defining and monitoring adequacy. The most prominent of these is urea kinetic modelling (UKM) which received considerable impetus from its

evaluation in the National Cooperative Dialysis Study (NCDS).^{250,251} A re-examination of this study²⁵² showed a lower morbidity in patients: (1) with a $K_t/V > 0.8$ (in thrice weekly dialysed patients), where K = total urea clearance (residual renal clearance plus clearance by dialyser (ml/minute), t = dialysis time (minutes), and V = the urea distribution volume (= total body water (ml)); and (2) with a protein catabolic rate (PCR) from 0.8 to 1.4 g/kg/body wt/day. PCR is derived from the urea generation rate and in stable patients is considered to be an index of the adequacy of protein intake. There is a strong correlation between K_t/V and PCR which may suggest that the poor control of the uraemic state resulting from inadequate dialysis causes the retention of appetite-suppressing uraemic toxins, resulting in malnutrition and increased morbidity and mortality.^{252,253}

UKM is becoming increasingly used to prescribe and monitor the delivery of haemodialysis. The targets are derived from the NCDS, that is, $K_t/V > 1.0$ and $PCR = 0.8-1.2$. Whilst it is widely recognized as a potentially useful tool there remain areas of concern. The choice of urea as a marker solute is subject to criticism, but there is no ideal marker solute,²³⁹ and urea at least has the advantage of reflecting protein catabolism, the products of which are central to the concept of uraemic toxicity. Its use also has the substantial backing of the NCDS.²⁵⁰⁻²⁵² Whilst the parameter K_t/V is becoming well accepted, the exact means of calculating it for routine clinical purposes still inspire debate.²⁵⁴⁻²⁵⁷ There is also some discussion about what constitutes an optimal target K_t/V for chronic haemodialysis patients and the view has been expressed that morbidity continues to decline with increasing K_t/V with no obvious optimum.²⁵⁸ The remarkable survival figures from Tassin,²⁵⁹ achieved with a mean $K_t/V = 1.67$, may constitute some support for this view, though there are other possible explanations including case-mix and control of hypertension. Whether the same target K_t/V is appropriate for stable chronic patients (such as those studied in the NCDS) and sicker, more catabolic patients is also unclear.²³⁹

The use of UKM to maintain adequacy when dialysis times are shortened can be highly beneficial.²⁶⁰ The safety margin though is small and rigorous monitoring is required to ensure adequate delivery. Rapid treatments may expose a further problem. The degree of post-dialysis urea rebound is greater after such treatments because of the limiting effect of intercompartmental shifts on urea clearance.²⁶¹ This effect will lead to underdialysis unless allowance is made by the appropriate timing of post-dialysis blood sampling or by modification of the single-pool based UKM parameters to account for these two-pool effects.²⁶¹ The dialysis membrane used may also have important effects.

Standard cellulosic membranes were employed in the NCDS. It has been suggested that high-flux dialysers with better biocompatibility characteristics require less rigorous urea clearance.²⁵³

Concern has also been expressed that the two major parameters derived from UKM are not independent since they are mathematically derived from similar parameters. This counsels caution in interpreting the correlation between them.²³⁹ Finally, and perhaps most importantly, the use of these criteria of adequacy are not yet supported by long-term studies with mortality as the end point. This will be the definitive test.

Adequacy of CAPD

In contrast to haemodialysis, the adequacy of CAPD has received little attention. Most patients on this treatment are prescribed a standard regime of 8 litres of fluid daily. Taking into account the wide range of patient size, and their considerable diversity in residual renal function, it would be surprising if there were not wide variations in dialysis adequacy. The available studies confirm that CAPD patients received a wide range of dialysis dose expressed as K_t/V .²⁶³⁻²⁶⁵

It is also apparent that dialysis adequacy declines with increasing time on dialysis, and that this is related to a decline in residual renal function²⁶³⁻²⁶⁵ rather than in the parameters of peritoneal mass transfer.^{264,265} There are also highly significant

correlations between K_t/V and PCR normalized for total body water.²⁶³⁻²⁶⁵

There are two related but major difficulties in interpreting UKM data in CAPD patients. First is its lack of validation by clinical outcome measures. Recently, however, three studies have demonstrated an inverse correlation of K_t/V and hospitalization rate.²⁶⁴⁻²⁶⁶ There are no studies relating CAPD adequacy and mortality. Secondly there is considerable debate on the values of K_t/V consistent with adequacy. Theoretical considerations based on the 'peak hypothesis'²⁶⁷ suggest that for CAPD to produce the same steady-state concentration of urea as the midweek prehaemodialysis concentration, a daily K_t/V of 0.3 is required (Figure 1). There is a paucity of data but patients with a daily $K_t/V < 0.25$ had significantly more hospitalizations than those with a higher K_t/V .²⁶⁵

A worrying feature is the finding of a decline of K_t/V with loss of residual renal function. There is a limited capacity in CAPD to compensate for loss of residual renal function by increasing dialysate volumes. This implies that there must be considerable doubt about the long-term viability of the technique especially in patients with larger than average body mass.

Other aspects of adequacy

The discussion above has been dominated by the concept of biochemical adequacy. There are clearly

Figure 1 Interrelationships of adequacy parameters in haemodialysis and CAPD. The saw-tooth line represents the blood urea concentration in a typical patient haemodialysed three times weekly with NPCR = 1 and $K_t/V = 1$. The horizontal lines represent the situation in CAPD patients with varying adequacy parameters. The horizontal solid line represents a daily $K_t/V = 0.2$, the dotted line a daily $K_t/V = 0.3$, and the dashed line a daily $K_t/V = 0.4$.

other aspects. Perhaps the most important of these is adequacy of control of salt and water balance and hypertension. There is evidence that in both short hours haemodialysis and CAPD that blood pressure control may be suboptimal and associated with progressive cardiovascular damage.^{268,269} The requirement for adequate control of hypertension may play a significant role in the design of optimal dialysis schedules. After all most dialysis patients die a cardiovascular death.

Dialysis-related amyloidosis

Dialysis-related amyloidosis is now recognized as a major, and potentially limiting complication of chronic dialysis treatment. The syndrome was recognized in the early 1980s²⁷⁰ and soon after β_2 -microglobulin (β_2 m) was identified as the amyloid precursor protein.²⁷¹ The main clinical features are carpal tunnel syndrome and destructive arthropathy, predominantly affecting large and medium-sized joints, and associated with bone cysts.²⁷² The spine is also involved though mechanisms other than amyloid deposition may be of importance in the pathogenesis of the spondyloarthropathy.^{273,274} The incidence of both carpal tunnel syndrome and the osteoarticular lesions increase with the duration of haemodialysis treatment. There is virtually 100% involvement by 15–20 years.^{275,276} Age at onset of dialysis is an important predictor, older patients being more likely to develop the problem.²⁷⁷ Visceral involvement occurs infrequently, but can have clinical consequences.²⁷⁸

The recognition of β_2 m retention as the essential requirement for the development of dialysis-related amyloidosis, has stimulated enquiry into factors affecting its rate of synthesis, release and clearance. β_2 m is an 11,800 dalton protein which, as part of the human class I major histocompatibility complex, is found on the surface of all nucleated cells. It is also found in neutrophil granules, and is a secretory protein of hepatocytes. Increased synthesis and release into extracellular fluid are mediated by various cytokines including tumour necrosis factor, interleukin-2, and alpha and gamma interferons. High serum levels occur in inflammatory and malignant lymphoproliferative disorders. It is eliminated from the body largely (95%) by glomerular filtration and subsequent tubular absorption and degradation, hence its accumulation in renal failure.

The possibility that dialysis specific factors may be important in the accumulation of β_2 m has received much attention. There is growing evidence that haemodialysis incites an inflammatory response, stimulating the cellular release of interleukin-1 and TNF, granulocyte activation with the generation of reactive oxygen species, and comple-

ment activation.^{279–281} In addition, there is *in vitro* evidence of increased β_2 m production by lymphocytes and monocytes harvested at the end of haemodialysis.²⁸² Many of these processes were more pronounced in or confined to dialysis involving cuprophane membranes when compared with dialysis involving newer, more biocompatible membranes, composed of polymethylmethacrylate, polyacrylonitrile or polysulphone. There is, however, very little evidence of β_2 m production during clinical haemodialysis when correction is made for dialysis-induced changes in extracellular fluid volume.^{283–286} As well as possible membrane effects on β_2 m production, the composition and purity of the dialysis fluid may also have a role, since acetate and endotoxin both promote interleukin-1 production.^{287,288}

Whilst doubts remain about differences between membranes with respect to their capacity to generate β_2 m, there is little doubt that a significant clearance of β_2 m can be achieved using high flux membranes compared to that achieved by cuprophane.^{289,290} As well as increased removal of β_2 m by filtration through these high flux membranes, there is also evidence of enhanced adsorption of β_2 m on to the membrane surface,^{289–291} an effect which may be modified by dialyser reprocessing techniques.²⁹¹ Increased β_2 m clearance by highly permeable membranes may well be clinically important, since a large multi-centre retrospective study has shown a decreased incidence of dialysis-related amyloidosis in patients dialysed using polyacrylonitrile compared to patients dialysed using cuprophane.²⁶⁷ Haemofiltration has a greater capacity to remove β_2 m than even high flux dialysis.²⁹²

Although experience with long-term CAPD is still limited, there are now a number of reports of dialysis-associated arthropathy occurring in patients treated solely by this modality,^{293–295} and reports of the disease progressing after transfer to CAPD from haemodialysis.¹⁸⁷ There is significant clearance of β_2 m by the peritoneal membrane,^{296,297} which is of the same order as that achieved by high-flux dialysis. Hypertonic exchanges,²⁹⁶ and the use of glucose polymer,²⁹⁸ both increase peritoneal clearance. There is no evidence of β_2 m generation during the dialysis process, though, like haemodialysis, CAPD can induce cellular activation and the release of inflammatory mediators.²⁹⁹ The propensity for CAPD patients to develop the dialysis-related amyloidosis may well be less than that for haemodialysed patients, at least those treated using standard cuprophane membranes, but only further studies will tell.

Recent work has provided further insights into the pathogenesis of the disease, and argues against the role of simple precipitation of β_2 m into amyloid-like fibril structures as the sole cause.

Amyloid fibrils seem to consist not only of intact $\beta_2\text{m}$, but also of proteolysed fragments, at least one of which has also been demonstrated in the plasma of long-term haemodialysed patients.^{300,301} Proteolysis of $\beta_2\text{m}$, perhaps by proteases released as part of the inflammatory response to haemodialysis, may be important in the development of the disease. On the other hand it has been argued that it is incomplete proteolysis of $\beta_2\text{m}$ which is the necessary condition for amyloid fibril formation, and that inhibition of proteolysis by 'amyloid enhancing factors' such as the anti-protease α_2 -macroglobulin predisposes to the condition.³⁰²

Treatment options are limited for established disease. Renal transplantation has been shown to limit disease progression²⁹⁴ but there is no other effective therapy. Prevention is therefore of the utmost importance. High-flux dialysis using bio-compatible membranes, bicarbonate as the buffer and ultrapure water seem rational measures to adopt.^{303,304} Haemodiafiltration offers the best hope of preventing the disease but is an expensive option with currently available technology. The place of CAPD in prevention strategies is presently unknown. Prospective studies are required to evaluate these options perhaps employing recently described radionuclide tracing and imaging of $\beta_2\text{m}$ amyloid deposits to monitor disease progression.³⁰⁵⁻³⁰⁷

Transplantation

Matching

Despite the absence of large randomized prospective controlled trials, HLA matching is now accepted as one of the prime determinants of both early and, increasingly importantly, long-term graft survival.³⁰⁸ It has also become clear that kidneys that undergo neither a rejection episode nor primary non-function do very much better than those that do.³⁰⁹ This observation has been advanced as a justification for intensive induction regimes usually including biological anti-lymphocyte preparations. The impact of DNA typing on transplantation is yet to be felt but graft survival of 90% may be attainable.³¹⁰ Although with DNA typing matching will become more difficult, it will be more exact.

New drugs

A variety of new immunosuppressive drugs is being studied both in animal models of transplantation and in pilot studies in man.³¹¹ It seems likely that some will soon find acceptance in routine clinical practice.^{311,312}

FK506

FK506 is a macrolide³¹³ which acts in a similar manner to cyclosporin A by blocking the phosphatase activity of calcineurin which leads to a failure of transcription of IL2 and other T-cell activation genes. Both cyclosporin A and FK506 enhance the transcription of TGF- β which is a potent inhibitor of IL2 stimulated T-cell proliferation. FK506 is more potent in these regards than cyclosporin A and is also a more potent inhibitor of B cells. Nephrotoxicity is a major problem but early reports suggest that hypertension is less of a problem with FK506. The impression is that FK506 may well replace cyclosporin A in liver transplantation but that it is unlikely to do so in renal transplantation. The results of several trials comparing FK506 and cyclosporin A should be available soon.

Rapamycin

Rapamycin³¹⁴ is also a macrolide and like FK506 binds to FK-binding protein, but this is not its mode of action. It blocks IL2-mediated signal transduction and can block IL2 driven T-cell proliferation. It does not block the induction of IL2 gene expression. It is synergistic with cyclosporin A but antagonistic to FK506. In rats it produces myocardial toxicity.

RS-61443

This agent³¹⁵ is a semi-synthetic derivative of a fungal antibiotic, mycophenolic acid. It is an inhibitor of purine synthesis, like azathioprine, which it may replace. It is synergistic with cyclosporin A and 15-deoxyspergualine. It does not appear to be marrow toxic. Its major side effects are on the gastro-intestinal tract.

15-Deoxyspergualin (15-DS)

This agent³¹⁶ is a derivative of spergualin from *Bacillus laterosporus*. Its mode of action is unknown. It suppresses macrophage function (interleukin 1 production, production of oxygen derived radicals, reduction of class II expression), and decreases cytotoxic T-cell proliferation. It appears more potent than cyclosporin A and may be synergistic with both cyclosporin A and FK506. 15-DS has been shown to reverse established rejections and to prevent their occurrence. It is toxic to bone marrow and may cause gastro-intestinal disturbances.

Table XV Antibodies being used in transplant rejection

Antibody	Mitosis	ADCC	Modulation	Lysis	N-K cells	Cytokine release	Cytokine release syndrome
ATG	–	++	?	±	↓↓↓	TNFα	++
OKT3	++	++	++	–	↓	TNFα, INFγ GMCSF IL2, 3, 6, 10	++++
T10 B9	±	±	++	+	→	TNFα, INFγ IL2	
CAMPATH-1	–	±	–	++	↓↓		++
33B3.1	–	+	?	–	→		–
SDZ CHI 621	–	+	+	–	→		–
SDZ CHH 380	–	+	++	–	→	TNFα IL6	+

TNFα = Tumour necrosis factor alpha; INFγ = gamma interferon; GMCSF = granulocyte monocyte colony stimulating factor; ADCC = antibody-dependent cell-mediated cytotoxicity; NK = natural killer; ATG = anti-thymocyte globulin.
– negative or absent; ± weak or equivocal; + positive or present; ↓ reduced; → no change; ↑ increased; ? unknown.

Table XVI Immunogenicity of antibodies being used in transplantation

Antibody	aID (%)	Immunogenicity aALLO/aXENO (%)	Half life (hours)	Specificities (CD)
ATG	–	70–80	?	HLA DR, LEU-C 45, 18, 2, 4, 8
OKT3	30–70	30–100	24	3
T10 B9	10	30–50	4	3
CAMPATH-1	?	80	8	W52
33 B3 1	30	80–90	24	25
SDZ CHI 621	0	0	312	25
SDZ CHH 380	1.3	4.5	77–151	7

HLA = Histocompatibility locus antigen; LEU-C = leucocyte common antigen; aID = anti-idiotypic antibody; aALLO = anti-allotypic antibody; aXENO = anti-xenotypic antibody; CD = cluster determinant.

New biologicals

Molecular biology is producing an increasing range of pure and specific animal antibodies to defined specificities on human lymphocytes.³¹⁷ These antibodies can be chimaerized or humanized.³¹⁸ This additional step, although increasing cost considerably, renders the end product either less or non-immunogenic. Some of the currently available antibodies are summarized in Tables XV and XVI.

Chimaeric antibodies

Anti-CD7 antibodies, although non-immunogenic, had no significant impact on either the number or onset of rejection episodes in first cadaveric renal allograft recipients.³¹⁹ Chimaeric anti-CD25 antibodies are currently being evaluated. Limited experience with anti-CD4 antibodies indicates that, although these reagents are very potent in animal models,³²⁰ they may elicit an anti-idiotypic response.

Other MOAB

Other reagents with effects on lymphocyte adhesion are being developed and evaluated, such as antibodies to CD2, CD8, LFA1, ICAM-1, LFA3. Development is still largely at the stage of animal studies although preliminary results with anti ICAM-1 (CD54) antibodies in humans appear promising.³²¹ The mode of action of these antibodies varies depending not only on the surface determinant against which the antibody is directed but also on whether or not the antibody is lytic, depleting or modulating (Table XV). Of considerable clinical importance is the cytokine release syndrome seen most markedly with OKT3. It now seems likely that antibodies causing the release of TNFα may also predispose to graft thrombosis.³²²

Optimal immunosuppression

There is still no agreement as to what is the optimal immunosuppressive regime for renal allografts.

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Strategies need to be developed that take into account an early induction phase, an intermediate semi-stable phase of graft acceptance and then a prolonged maintenance phase during which drug toxicity may well be more important than the risk of rejection.

Induction

The use of a monoclonal anti-CD25 antibody for induction is promising for first transplants.³²³ Second or subsequent transplants may benefit from the use of the more widely reactive polyspecific antibody such as anti-thymocyte globulin. Induction should be tailored in the light of the relative risk of early rejection. Fully matched first grafts have a much lower risk of rejection than poorly matched grafts or second or subsequent transplants. Transplants into the highly sensitized recipient also have an increased risk of early rejection. By targeting the early activation steps of the immune response, using agents effective only against activated lymphocytes, a degree of specificity can be obtained which should not result in an unacceptably high risk of infection.

Maintenance therapy

Cyclosporin A usually with prednisolone and azathioprine, is the most widely accepted maintenance regime for both the early and intermediate period after grafting. The best regime for long-term therapy is not clear. Steroids can be withdrawn safely in some patients.³²⁴ Cyclosporin A can be stopped, particularly in those in whom marked or progressive nephrotoxicity is a problem, but there does appear to be a significant risk of rejection episodes occurring in these patients.³²⁵

Treatment of rejection crises

Steroids still remain the mainstay of treatment of early rejection crises, because of the ease of administration and cost. OKT3 can be used successfully for the treatment of rejection and for the rescue of patients from steroid-resistant rejection crises.³²⁶ Polyclonal anti-lymphocyte or anti-thymus globulin similarly can be used for rescue. Anti-CD25 antibodies do not appear effective for the reversal of rejection episodes.³²⁷

Long-term medical management of renal transplants

The principal cause of death after successful transplantation is a cardiovascular or cerebrovascular event. It is now time that transplant physicians assessed cardiovascular risk factors more thoroughly. It is interesting to note that not only are many transplant patients hypercholesterolaemic but that lipoprotein-a is also markedly elevated.³²⁸ Preliminary studies suggest that cyclosporin A may be particularly prone to raise lipoprotein-a. Interactions (for example, rhabdomyolysis) between lipid lowering agents and cyclosporin A have to be borne in mind when prescribing.

Long-term medical management of renal transplants must include a determined attempt to reduce and stop smoking, obsessional blood pressure control, using agents not associated with dyslipidaemias and diet. These measures may well help to retard or even prevent chronic vascular rejection which has many pathogenetic similarities with atherosclerosis. An up-to-date review of the common ground between atherosclerosis and chronic vascular rejection can be found in the proceedings of the Fourth Alexis Carrel Conference.³²⁹

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