Reviews in Medicine

Nephrology, dialysis and transplantation

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Introduction

This review highlights some of the more important advances that have been made in renal physiology, nephrology and renal replacement therapy. There have been dramatic advances in our understanding of the molecular mechanisms in physiology, pathology and in the pharmacology of immunosuppression. We understand better the factors that lead to the relentless progression to end stage renal failure in conditions where the original or specific disease may well be inactive. Intervention is now possible to slow progression.

Long term dialysis has produced its own special problems and increased ingenuity and improved biotechnology are required. The revolution occurring in genetic engineering is paying its dividends to the dialysis populations through the remarkable benefits of human recombinant erythropoietin. The elusive goal of transplantation without infection or rejection remains a distant objective but developments in monoclonal antibody production and the early claims for FK506 are rapidly being put to the test.

Renal physiology

(A) Tubular function

(i) Tubular transport mechanisms

The concept of membrane cotransport is almost 30 years old.¹ The process is now considered to be virtually ubiquitous. 'There are no primary active transport processes but for some cations. Other accumulative transport is always secondary active via co-transport with sodium (and/or counter-transport with potassium).'² These remarks conclude the introduction to a symposium on the subject (Cotransport mechanisms in renal tubules, 1989),^{2a} which reviews recent developments in the

sodium-coupled transport of glucose, amino acids, phosphate, and organic anions. Urate transport (coupled only indirectly to sodium via urate-anion counterexchangers), chloride-bicarbonate exchangers (there are separate sodium-dependent and sodium-independent systems and bicarbonate may also be cotransported electrogenically with sodium), the basolateral potassium-chloride cotransporter, and $\text{Na}^+:\text{K}^+:\text{2Cl}^-$ cotransport in the thick ascending limb are among other topics addressed. Most notably, the DNA for the intestinal Na^+ -glucose carrier has been cloned and sequenced,^{3,4} a chloride-formate exchanger may play a major role in electroneutral sodium chloride reabsorption in the proximal tubule,⁵ and thiazide-sensitive sodium chloride cotransport has been confirmed in the early distal tubule.⁶

The different segments of the nephron have their particular transporting properties by virtue of the specific transporter proteins, active ion pumps and channels that are distributed in a highly organized system in membranes of the tubular cells. The system works to transport specific substances from either the luminal fluid or the capillary as these transporting mechanisms are asymmetrically orientated with fixed differences between the luminal membrane and the basolateral membranes. The movement of molecules is down electrochemical gradients generated by the ubiquitous $3\text{Na}^+/\text{2K}^+ - \text{ATPase}$ pump located in the basolateral membrane. Figures 1 to 6 summarize the current view on the distribution of these transporter functions in different segments of the nephron.

There has been some debate on the relative importance of kidney and liver in systemic acid-base balance.^{7,8} The cellular and molecular aspects of renal hydrogen ion transport have been reviewed,⁹ and the role of proton pumps emphasized.¹⁰ An interesting concept of the kidney's role in acid-base balance has emerged. In order to achieve acid-base balance the kidney must synthesize 'new' bicarbonate to replace that

Figure 1 Explanatory key for Figures 2 to 6.

Figure 3 Thick ascending limb of loop of Henle (TALH).

Figure 2 Proximal tubule.

Figure 4 Early distal tubule.

Figure 5 Late distal tubule.

Figure 6 Collecting tubule.

which has been consumed in the buffering process. A minority of 'new' bicarbonate is formed by the titration of hydrogen ions with filtered HPO_4^{2-} in the tubular fluid. The majority is formed by the metabolism of glutamine (an organic anion whose production does not also yield protons) to NH_4^+ and bicarbonate in proximal tubular cells. Excretion of this NH_4^+ (via the Na^+ - NH_4^+ antiporter) is a necessary step to ensure net gain of bicarbonate since, if retained, NH_4^+ is converted by the liver to urea, a process which consumes bicarbonate. In this view the renal ammonium system is critically involved in the generation of 'new bicarbonate'. Proton secretion whilst essential to maintain acid-base balance is essentially involved in reclamation and recycling of tubular bicarbonate.¹¹

The renal ammonium system is thought to play an important role in the response to chronic metabolic acidosis in some situations including chronic renal failure,¹² and increased concentrations of ammonia are found in the renal cortex of the remnant kidney.¹³ There is some evidence that this may have a role in the progression of renal failure possibly by activation of the alternative complement pathway.¹⁴

The renal handling of calcium has been re-examined.¹⁵ Whether vitamin D metabolites have any significant effect on renal calcium handling remains a controversial issue. Recently a vitamin D dependant 28-kDa-calcium binding protein and Ca^{++} - Mg^{++} ATPase have been found to be co-localized in the distal convoluted tubule of the human kidney,¹⁶ which suggests a possible role for vitamin D on calcium transport at this site.

(ii) Clinical aspects of tubular dysfunction

Clinical disorders of renal tubular phosphate transport have been reviewed by Levi.¹⁷ The genetic defect in the commonest of these disorders, X-linked hypophosphataemic rickets, has recently been localized to the Xp22 chromosomal band.¹⁸ Furthermore, in the murine counterpart of this disease recent work with parabiosis suggests that a humoral factor which is distinct from parathyroid hormone may be associated with the defect in renal tubular phosphate reabsorption.¹⁹ A large series of patients with Bartter's syndrome with a 10 year follow-up has been reported emphasizing its essentially benign nature.²⁰ Most patients presented with incidentally discovered hypokalaemia which was rarely fully correctable by treatment. Another report²¹ draws attention to the high prevalence of nephrocalcinosis in Bartter's syndrome.

(iii) Hormones and tubular function

(a) **Aldosterone** It is now well established that the antinatriuretic and kaliuretic actions of aldo-

sterone are principally centred on the distal tubule and cortical collecting duct. There is much uncertainty though about its actions at the cellular and molecular levels. A two-step mechanism of action via early and late aldosterone-induced proteins (AIPs) has recently been suggested.²² At 1–3 hours after aldosterone application early AIPs are formed which may include the enzymes methionine adenosyltransferase and *S*-adenosylhomocysteine-transferase. These enzymes cause an increase in the intracellular *S*-adenosylmethionine level which may in turn be responsible for the increased activity of methyltransferases. Increased methylation of the protein moiety of the sodium channels in the apical membrane causes an influx of sodium. The resulting increase in intracellular sodium causes increased activity of pre-existing Na/K-ATPase in the basolateral membrane, with increased sodium output. At 4–24 hours, aldosterone increases the synthesis of late AIPs including newly synthesized subunits of Na/K-ATPase which are duly integrated into the basolateral membrane. That there are two aldosterone receptors with different affinities may support this concept, though early AIPs could activate other genes coding for late AIPs.

(b) *Natriuretic hormones* This has been an area of intense activity, and a vast amount of data has been accumulated and subjected to critical review.^{23–25} Most attention has been directed at the recently discovered atrial natriuretic peptide (ANP) but

there are many other contenders for the title of natriuretic hormone. These include one or more endogenous digitalis-like compounds, circulating lysophospholipids, and gamma-melanocyte-stimulating hormone, which has recently been discovered to be responsible for the natriuresis which immediately follows unilateral nephrectomy in the rat.²⁶

ANP undoubtedly has potent natriuretic properties which derive from a variety of systemic and intrarenal effects (Table I). Nevertheless its precise physiological and pathophysiological role remains unclear. It has been suggested that it is the major mediator of the natriuresis caused by acute, large plasma volume expansion in humans and in anaesthetized rats²⁴ and that it may contribute in varying degrees to the natriuresis in other situations. Elevated plasma levels of ANP have been found in a wide variety of pathological states including congestive cardiac failure, cor pulmonale, acute and chronic renal failure, atrial tachydysrhythmias, the syndrome of inappropriate ADH secretion (all reviewed by Weidmann²⁷) and in poorly controlled diabetics.²⁸ Levels in the nephrotic syndrome²⁹ and in decompensated cirrhotics³⁰ are normal or high, depending on intravascular volume status and renal function. The therapeutic potential of ANP infusions has been explored in some of these states. In heart failure, activation of the renin-angiotensin system, and diminished renal perfusion, effectively block a natriuretic response.²⁵ ANP seems to retain its diuretic and natriuretic

Table I Systemic and renal effects of atrial natriuretic peptide

<i>Parameter</i>	<i>Effect</i>	<i>Mechanism</i>
<i>Systemic</i>		
Blood pressure	↔ low dose ↓ high dose	1. vasodilatation due to antagonism of vasoconstrictive effects of AII and noradrenaline. 2. reduced blood volume due to extravascular fluid shifts.
Sympathetic activation	↑ heart rate ↑ lipolysis	Baroreceptor stimulation.
<i>Hormone interactions</i>		
Aldosterone	↓	inhibits secretion.
Cortisol	↔ ↓	inhibits secretion.
Renin	↓ low dose ↑ high dose	inhibits secretion. indirect stimulation via systemic effect.
AVP	↔ ↓	? pituitary effect.
<i>Renal</i>		
Glomerular filtration	↑	afferent arteriolar dilatation
Filtration fraction	↑	efferent arteriolar constriction
Renal blood flow	↔	increased K_f .
Medullary blood flow	↑	unknown.
Tubular reabsorption of sodium	↓	direct effect on inner medullary collecting duct through amiloride sensitive pathway.

AII = angiotensin II, AVP = arginine vasopressin. K_f = ultrafiltration coefficient. ↑ increase ↓ decrease
↔ no change

activity in patients with chronic renal insufficiency³¹ and in some patients with the nephrotic syndrome.³² In decompensated cirrhotics, as in severe heart failure, the infusion produced a profound fall in blood pressure and glomerular filtration rate.³³ There is a hint of possible therapeutic potential. Experimental studies in acute renal failure suggest that administration of ANP before or immediately following the renal insult has a substantial renal protective effect.^{34,35}

(B) Renal haemodynamics

There are a number of mechanisms involved in the regulation of renal blood flow including intrinsic myogenically mediated responses of preglomerular vessels, tubuloglomerular feedback (TGF) mechanisms, and a plethora of systemic and locally synthesized hormones which act on the renal vasculature. A recent model of renal vascular resistance control attempts to integrate these mechanisms.³⁶ It considers that under normal conditions the resistor segments of the renal vascular tree maintain a spontaneous resting tone which is susceptible to a degree of modulation by, but is not regulated by, vasoactive hormones. The net effect of the 'hormonal soup' to which the system is exposed is to stabilize it rather than control it. Hence inhibition of one of these hormonal systems does not vary the resistance but may impair its response to perturbations by some other mechanism (such as the effect of non steroidal anti-inflammatory agents on renal haemodynamics in conditions of volume depletion). The model considers the renal resistance system to be composed of three discrete components, a preglomerular myogenically regulated system, a TGF-controlled system localized at the preglomerular vascular pole, and immediately downstream from the former. The third component is the post-glomerular system which is assumed to function like a passive flow resistor. The systems are arranged in series and interact haemodynamically. Thus a decrease in the TGF-controlled resistance causes an increased blood flow at this point. This causes a steep drop in hydrostatic pressure along the myogenically controlled segment immediately upstream, thus inducing dilatation of this segment. Hence the TGF-mediated change has been amplified by the myogenic mechanism.

There have been other contributions to this field. A substantial number of papers continue to explore the effects of various hormones and mediators on glomerular haemodynamics. Of interest are the observations that the haemodynamic effects of growth hormone seem to be mediated by insulin-like growth factor 1,^{37,38} that platelet activating factor reduces renal vascular resistance and increases glomerular permeability³⁹ and that calci-

tonin gene related peptide causes relaxation of mesangial cells and decreases renal vascular resistance.⁴⁰ The function of the interlobular artery has also been reviewed, and it may well be important in renal autoregulation.⁴¹ Of clinical interest is a review of the renal haemodynamic consequences of angiotensin-converting enzyme inhibition in congestive cardiac failure.⁴² Factors predisposing to a decline in renal function included an initial sustained fall in blood pressure, intravascular volume depletion and an activated renin-angiotensin system, and a relatively high fixed dose of enalapril. The use of shorter acting agents in patients at risk of renal impairment was recommended.

Acute renal failure

(i) Incidence and prognosis

The persistently high mortality from acute renal failure (ARF) despite technological advances has been attributed to changing patterns of disease in an aging population.^{43,44} A large-scale recent series of 1347 patients accumulated over 30 years has allowed fresh examination of these issues.⁴⁵ The case-mix did indeed dramatically alter over the time frame, with a decline in low risk obstetric and traumatic cases and a substantial increase in the number of elderly patients with high risk medical and surgical conditions. A substantial increase in rapidly progressive glomerulonephritis, often in the context of systemic disease, was noted. Median age rose markedly from 41 years in the 1950s to 60 years in the 1980s. Interestingly, despite these changes, survival improved progressively from 48.8% in 1956–59 to 57.9% in 1985–88. The improvement in survival in medical and surgical cases looked even more impressive (38.5% to 57.9% in the same time periods). Improvements were attributed to better management of complicated ARF especially that due to intrinsic renal disease. The pattern of ARF is also changing in some developing countries with a declining proportion due to obstetric problems, diarrhoeal illnesses and intravascular haemolysis, and an increasing proportion due to sepsis, drugs and surgery.⁴⁶

Many patients with ARF also have acute respiratory failure requiring ventilation (40% of the patients in the study of Turney *et al.*⁴⁵) The prognosis in such cases remains poor. It is even poorer in cases with greater degrees of organ failure, and as the prognosis plummets the expense of the treatment escalates. There are obvious and as yet unsolved dilemmas regarding patient selection. It is clearly important to identify with a sufficient degree of certainty those patients with multiple organ failure most likely to benefit from prolonged intensive care. APACHE II (acute physiology and

chronic health evaluation) scores on admission correlated well with survival in 90 ARF patients, 88 of whom required ventilation.⁴⁷ There were no survivors in patients with scores of >40 , but there were too few patients in this category to extrapolate that treatment is futile. Liano *et al.*⁴⁸ used a multiple linear regression model to calculate a discriminant score in 228 cases of ARF according to the presence or absence of 4 variables (oliguria, assisted respiration, hypotension, and coma) when the patient was first seen. There were no survivors from among the 22 patients with discriminant scores of >0.856 . The urgent need for more such studies has been emphasized.⁴⁹

The prognosis for renal function in survivors has also been addressed. Glomerular filtration rate, and tubular handling of sodium, glucose, phosphate and amino acids were normal in all 10 patients tested 7–12 years following an episode of ARF in childhood. Filtration fraction though was elevated in 6 of 8 patients, testifying to abnormal glomerular haemodynamics, a consequence perhaps of previous nephron loss.⁵⁰

(ii) Causes

(a) *Aminoglycoside nephrotoxicity* ARF is frequently multifactorial and in the general hospital setting, drugs, particularly aminoglycoside antibiotics, and radiographic contrast agents, have frequently been incriminated. Gentamicin chronically infused into rats in doses low enough to maintain plasma levels at less than the generally acceptable trough levels or even in the undetectable range, caused a gradual decrement in inulin clearance to 50% of control levels by 6 months and a chronic interstitial nephritis.⁵¹ Interestingly both renal function and histology continued to progressively decline after cessation of treatment. These observations and the marked dissociation between inulin and creatinine clearances noted during the study, question the generally accepted monitoring standards.⁵² The development of rapid assays of urinary peptide level or brush border antigen are advocated as sensitive indicators of nephrotoxicity.⁵³ It is also worth a thought that gentamicin nephrotoxicity has been shown to be potentiated by a focus of tissue necrosis.⁵⁴

(b) *X-ray contrast nephrotoxicity* There have been two prospective controlled studies on the effects of contrast agents on renal function. Diabetics with pre-existing renal insufficiency were confirmed to be at significant risk of clinically important contrast-induced nephropathy (50% increment in serum creatinine), though the incidence was less than previously reported at about 9%.⁵⁵ Non-diabetics with renal insufficiency had less risk (5.5%) of milder deterioration (25%

increment in serum creatinine). In another study there was no difference between nonionic and ionic contrast agents in terms of their propensity to produce nephrotoxicity.⁵⁶ Close attention was paid to the state of hydration in both of these studies and many patients received intravenous hydration. Patients with myeloma are particularly susceptible to contrast as illustrated by a report of ARF occurring in a patient with this condition who received oral contrast for cholecystography.⁵⁷

(c) *ARF in bone marrow transplantation* A growing number of patients with haematological malignancies develop ARF, and dialysis requiring ARF has recently been reported in 24% of bone marrow transplanted patients.⁵⁸ Its development was presaged by jaundice, weight gain, amphotericin B usage, septicæmia, and hypotension. Its prognosis is poor with a mortality of 84%.

(d) *Haemolytic uraemic syndrome* In the epidemic form of haemolytic uraemic syndrome in children a diarrhoeal prodrome precedes the development of the disease. A particular strain of *Escherichia coli* (serotype O157:H7) is identifiable in the stool of these children. In other parts of the world, for example in South America and the Indian Sub-continent, *Salmonella* and *Shigella* have been implicated. These bacterial species produce toxins capable of fixing to and damaging the endothelial cell. In the case of *E. coli* the toxin is verotoxin.⁵⁹ In the haemolytic uraemic syndrome and presumably also in related conditions such as thrombotic thrombocytopenic purpura, post-partum acute renal failure, accelerated phase hypertension and the scleroderma crisis, endothelial damage leads to a thrombotic microangiopathy and the development of the well known clinical and biochemical features of these diseases. In most cases treatment is supportive with control of blood pressure and early dialysis. The infusion of large volumes of fresh frozen plasma (but not human albumin), either by simple infusion or by plasma exchange in the oliguric patient, will turn off the microangiopathy and may preserve renal function.⁶⁰ Prostacyclin infusion may be of additional benefit although proof is lacking. The difficulty lies in deciding which cases require aggressive treatment and which will recover with simple supportive therapy only. In general older children and adults and isolated or sporadic cases without a diarrhoeal prodrome probably warrant full therapy. How fresh frozen plasma works is not clear. Suggestions include supplying missing substrates for PGI₂ synthesis, restoration of enzymes capable of breaking up abnormal factor IIX von Willebrand macromolecular complexes and supplying enzymes which stabilize the complex clotting mechanisms.

(e) *Hepato-renal syndrome (HRS)* The hepato-renal syndrome gets little discussion in many books as it heralds end stage liver disease and cannot easily be pharmacologically reversed. However, with the advent of liver transplantation renal physicians will be asked to support more of these patients pending liver transplantation, particularly if the hopes raised by FK506 as a new immunosuppressive agent are fully substantiated. The hepato-renal syndrome develops in patients with pronounced systemic vasodilatation with systemic as well as portal shunting of blood.⁶¹ Systemic vascular resistance is markedly reduced. The acute renal failure occurs with intense intrarenal vasoconstriction yet with marked peripheral vasodilatation. The vasodilatation, shunting and reduced systemic vascular resistance render the effective arterial blood volume inadequate. This in turn leads to the stimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone system and AVP release. The hepato-renal syndrome may be viewed as an exaggerated attempt to preserve arterial blood volume in a situation where the arterial side of the circulation can never be replete because of the shunts and vasodilatation. What mediates the systemic vasodilatation is unclear although glucagon is a likely contender. The intrarenal vasoconstriction may be multifactorial with angiotensin II, catecholamines, reduced prostaglandins and bradykinin being suggested. Endotoxin, tumour necrosis factor and the recently described endothelial derived relaxing factor and endothelin may all play a role. In the short term, immersion to the neck in water (which expands the intravascular volume without altering its composition) together with a noradrenaline infusion will provoke a diuresis in these patients.⁶² Ornithine vasopressin (a vasoconstrictor analogue of AVP) may also be effective.⁶³

(iii) *Pathogenesis of acute tubular necrosis*

Much recent attention in this area has been focused on the seeming paradox of the kidney's unique susceptibility to hypoxic insult in the face of the undoubted richness of its blood supply. Solutions have concentrated on two main approaches. Firstly, an exploration of the inhomogeneity of oxygen supply and requirements within the kidney and particularly within the medulla, and secondly an examination of the potential role of activated oxygen species in mediating ischaemic and post-ischaemic injury.

Tubules and vessels of the medulla are distributed in hairpin arrangements to facilitate counter-current exchange of solutes and allow efficient concentration of urine. Oxygen is able to diffuse directly between arterial and venous limbs of the vasa recta resulting in strikingly low oxygen con-

centrations in medullary tissues. The osmotic gradient within the medulla is generated by active transport of sodium chloride by the thick ascending limb of Henle's loop (mTAL) which requires large amounts of energy. The low oxygen content of medullary blood and the constraints on medullary blood flow imposed by the requirement to maintain the concentration gradient ensure that the mTAL always operates on the edge of hypoxia. During an ischaemic insult therefore critical hypoxia leading to selective necrosis of the mTAL readily results and has been demonstrated in many animal models (for review see Brezis⁶⁴).

A reduction of the oxygen requirement of the mTAL by pharmacological blockade (e.g. with frusemide) or by reducing GFR (e.g. by hyperoncotic albumin infusion) has been shown to prevent mTAL damage. Regulatory mechanisms to protect the vulnerable mTAL from ischaemic injury have been hypothesized. Adenosine, a product of high energy phosphate metabolism, accumulates in ischaemic conditions and down-regulates transport in mTAL, increases medullary oxygenation by improving vasa recta flow and reduces GFR by augmenting tubuloglomerular feedback. Prostaglandin E₂ also reduces transport in the mTAL and enhances medullary blood flow, and other arachidonic acid derivatives may have similar effects. The unravelling of these intricate mechanisms may produce viable strategies for treatment and prevention.

Ischaemia and subsequent reperfusion is a potent stimulus to the production of free radicals,⁶⁵ the former by the mitochondrial respiratory mechanism and the latter by oxidation of hypoxanthine (an end product of high energy phosphate metabolism) by xanthine oxidase, a reaction which yields superoxide. Free radicals damage tissue principally by peroxidation of lipids, with resultant membrane destruction. The mTAL is clearly ripe for free radical induced damage.⁶⁶ It is exquisitely vulnerable to ischaemia and its high energy requirement ensures a rich substrate of hypoxanthine for free radical production on reperfusion. There is some experimental evidence to suggest that free radical-induced damage may be a factor in ARF, since glutathione, an endogenous free radical scavenger, and desferrioxamine both protect against postischaemic injury in the rat.^{67,68}

(iv) *Management*

Patients with acute renal failure are usually very ill and frequently managed on the Intensive Therapy Unit. For such patients the recently introduced techniques of continuous arterio-venous haemofiltration or haemodiafiltration (CAVH or CAVHD) are ideal.⁶⁹ Figure 7 illustrates the extracorporeal circulation required. The advantages of these tech-

Figure 7 CAVH and CAVHD.

niques are simplicity, the lack of sophisticated equipment, smooth control of fluid balance and little cardiovascular instability. CAVH is seldom adequate for renal replacement in hypercatabolic patients achieving a creatinine clearance of 10 ml/min if 600 ml/hour of filtrate is being removed.⁷⁰ CAVHD on the other hand with a dialysate flow rate of about 2 litres/hour will produce a creatinine clearance of about 30 ml/min.⁷¹⁻⁷³ Provided safe good vascular access can be achieved these techniques are applicable to any general intensive care unit. Although vascular access can be gained by femoral artery and femoral vein catheterization using the Seldinger technique, in older patients an arm Scribner shunt is preferable for fear of compromising lower limb circulation. The arteriovenous shunt is less likely to get infected than long term venous or arterial catheters. The membranes that are used in these filters are synthetic, highly biocompatible and very permeable, for example polysulfone, polyacrylonitrile. This technique has now all but replaced the need for intermittent haemodialysis on the intensive care ward. Although claims have been made that these techniques may improve survival, confirmation is still awaited.^{74,75}

(v) Hypercatabolic states

ARF is characterized by a hypercatabolic state. Underlying illness such as sepsis, trauma, or circulatory failure is important in this but uraemia itself commonly causes net protein catabolism, as does dialysis. Increased proteolytic activity has been demonstrated in uraemic plasma, and endocrine disturbances, accumulation of uraemic toxins and acidosis, may promote this. Glucocorticoid inhibitors block experimental uraemic proteolysis and abolish proteolysis induced by metabolic acidosis.⁷⁶ Therapeutic manoeuvres in ARF aimed at reversing this catabolic state by supplying glucose and amino acid infusions have proved generally ineffective and no convincing effects on mortality have been demonstrated.⁷⁷ Excessive doses of amino acids should probably be avoided since nephrotoxic effects have been reported experimentally. Treatment with essential amino acids and glucose rather than mixtures of essential and non-essential amino acids confers no benefit. Branched chain amino acids offer theoretical attractions, being the only amino acids primarily oxidized in skeletal muscle producing energy and nitrogen for synthesis of alanine and glutamine. Levels are low in ARF patients. Anticatabolic effects of these agents have been demonstrated though the current experience is small.⁷⁷

Glomerulonephritis

(i) Aetiology

Conventionally, glomerulonephritis is viewed as an immunological disease with damage to the glomerulus being produced either by the presence of immune complexes or deposits of anti-glomerular basement membrane antibody in the glomerulus. Some diseases do not lie comfortably with this simple classification, e.g. minimal change glomerulonephritis, focal segmental glomerulosclerosis and mesangiocapillary glomerulonephritis. In some cases of crescentic glomerulonephritis there may be little or no immune reactants (immunoglobulin and complement) in the glomeruli. It now seems likely that the so called immune complex diseases result more from the assembly of immune complexes within the glomerulus rather than from the deposition of pre-formed complexes from the circulation. The evidence for this comes from the animal studies in the rabbit using cationic antigen.⁷⁸ As yet we do not have insights into what may be the cationic antigens (or in some cases perhaps it may be that cationic antibody fixes first) involved in human disease. Other possibilities are clearly being sought. It is being queried whether or

not there is a human equivalent of the Heymann model of glomerulonephritis where antibodies react with an epithelial antigen on the podocytes which then caps and is shed to form sub-epithelial immune complexes producing a classical membranous type of glomerulonephritis.

Non-Goodpasture antibodies have been demonstrated in patients with glomerulonephritis. They appear to be quite common. These antibodies are to antigens that are different from the Goodpasture antigen (i.e. not the globular domain of Type IV collagen), and are found in systemic lupus erythematosus and the vasculitides as well as in mesangial IgA disease. They may represent anti-laminin antibodies.⁷⁹

(ii) *AIDS-related glomerulopathy*

Not all studies have clearly demonstrated glomerular lesions associated with the acquired immunodeficiency syndrome (AIDS). Differences may be explained partly on the basis of race and partly on whether or not there is associated hepatitis B or intravenous drug abuse.⁸⁰ There is no doubt that some patients with AIDS, as many as 30% in some studies, develop heavy proteinuria in excess of 2 g/24 h. Some of these patients have had a rapid downhill course to renal failure.⁸¹ Focal segmental glomerulosclerosis has been clearly related to drug abuse both before and after AIDS.⁸²

(iii) *Treatment of glomerulonephritis*

Immunosuppression remains the mainstay of therapy for glomerulonephritis and is variably successful depending on the histological lesion and the context in which the glomerulonephritis develops. Current treatment is summarized in Table II. Regrettably there is a great lack of adequate controlled trials on which to base recommendations for treatment.

Cyclosporin A has been used in a wide variety of different types of glomerulonephritis. Remission can be predictably induced in the minimal change disease (steroid responsive) but much less frequently or predictably in focal segmental glomerulosclerosis.⁸³ Cyclosporin A does not induce lasting remissions such as those associated with cyclophosphamide but does have a marked steroid sparing effect. Data are insufficient in other histological types of glomerulonephritis. It is important to remember that cyclosporin A is nephrotoxic so that long term use in glomerulonephritis is difficult. Furthermore glomerulonephritis recurs in the post transplant setting in patients treated with cyclosporin A, for example, mesangial IgA disease, focal segmental glomerulosclerosis and mesangio-capillary glomerulonephritis.

Studies on membranous glomerulonephritis suggest that subgroups of patients may benefit from treatment. Immunosuppression appears to benefit

Table II Drug treatment of idiopathic glomerular disease

<i>Lesion</i>	<i>Therapy</i>	<i>Reference</i>
Minimal change	Steroids	
	Alkylating agents	
	Cyclosporin A	83
Membranous GN	Steroids	84
	Cycles of chlorambucil and steroids	85
Focal segmental GS	Trial of steroids + / - alkylating agents	
Endocapillary proliferative GN		
Mesangial proliferative GN (eg mesangial IgA disease)	Steroids	91, 92
Diffuse proliferative GN (post infectious)	General supportive therapy	
Mesangiocapillary GN	Antiplatelet agents	93
Focal necrotizing GN and/or	Pulse methylprednisolone Immunosuppression Plasma exchange in selected cases	106
Crescentic GN		
		107

GN = glomerulonephritis. GS = glomerulosclerosis

those patients with particularly heavy proteinuria and a decline in glomerular filtration rate.⁸⁴⁻⁸⁶ Trials are difficult to construct as some 50% of patients with membranous glomerulonephritis remit spontaneously or remain stable for many years. A recent large retrospective study of 334 patients with membranous glomerulonephritis reports a 5 year kidney survival of 88% and a 10 year kidney survival of 77%.⁸⁷ This study suggests that marked tubulointerstitial disease, hypertension and advanced changes on electron microscopy as well as an elevated plasma creatinine at presentation are adverse prognostic features.

Mesangial IgA disease is probably one of the commonest forms of acute glomerulonephritis, particularly in young adults. Prognosis is not as good as was once thought with up to 25 to 30% of cases progressing to end stage chronic renal failure.⁸⁸ The lesion may also recur in renal transplants to cause graft loss. Since the majority of patients do well, trials of therapy are clearly also difficult to carry out. An Australian trial involving 37 patients was unable to show any benefit from eicosapentaenoic acid therapy over 2 years.⁸⁹ Treatment with cyclophosphamide and anticoagulants is claimed to improve long term outlook⁹⁰ but many would disagree with the use of this potentially toxic regime in a disease which usually has a good prognosis. Alternate day prednisolone in 6 children thought likely to do badly resulted in stable or improved renal biopsies and a normalization of urine tests and plasma creatinine.⁹¹ A larger Japanese trial also suggested that long term steroids may be helpful.⁹²

The situation with mesangiocapillary glomerulonephritis (MCGN) is also confused. A recent review of the trials carried out in MCGN gave support to the use of anti-platelet agents.⁹³

Much can be done by way of general supportive therapy to ameliorate the progressive nature of many types of glomerulonephritis. Dietary measures such as low protein and sodium restriction help to reduce both glomerular and systemic hypertension. The control of lipids in patients with persistent nephrotic syndrome is now achievable with newer drugs.⁹⁴ Although lipid lowering drugs ameliorate glomerulonephritis in animal models this has yet to be established in long term human studies. Even for patients with the nephrotic syndrome a high protein diet is no longer recommended as such diets increase renal blood flow, glomerular blood pressure and exacerbate proteinuria.⁹⁵ Angiotensin converting-enzyme blockers can reduce proteinuria, presumably as a consequence of a fall in intraglomerular blood pressure following efferent arteriolar relaxation. Though not established by long term trials, ACE blockers may be the preferred form of anti-hypertensive therapy for all forms of glomerular disease.⁹⁶

The multisystem vasculitides

The multisystem vasculitides that are commonly associated with significant glomerulonephritis are summarized in Table III. So called idiopathic focal necrotizing and crescentic glomerulonephritis are considered in this grouping of the multisystem vasculitides as many now feel this is more appropriate.

(i) Systemic vasculitis

Prolonged follow-up in systemic lupus erythematosus has shown that patients receiving cyclophosphamide^{97,98} do better than those on other regimes. It has also been claimed that for any severe vasculitis cyclophosphamide is to be preferred to azathioprine to gain remission. This may take 6 to 8 weeks. During this period plasma exchange is sometimes added in particularly fulminating cases. Thereafter maintenance therapy with prednisolone and azathioprine is usually offered. Cyclophosphamide remains the treatment of choice for Wegener's granulomatosis and is usually continued for several years as relapses are very common. Cyclosporin A has been studied in SLE and appears to have a beneficial effect on active disease in addition to allowing lower doses of steroids. Nephrotoxicity makes long term therapy hazardous.⁸³

Over the last few years experience has grown with the ANCA assay (anti-neutrophil cytoplasmic antibody). The test is of diagnostic value and also helps to assess disease activity in both microscopic polyarteritis and Wegener's granulomatosis.^{99,100,100a} Human antibodies to the Wegener's antigen and a monoclonal antibody directed against a highly purified preparation of this antigen react specifically with the epithelial and endothelial cells but not mesangial cells from cultured human glomeruli. This suggests a possible aetiological role for ANCA as the antibody appears cytotoxic in cell culture.¹⁰¹

Duration of immunosuppressive therapy is an unresolved and difficult question. In diseases with clear clinical and laboratory indices of activity treatment can be tailored to activity and in some cases may be safely stopped. However relapses can occur, cannot always be predicted and may be fulminating.^{102,103} Careful and prolonged follow-up is clearly required.

(ii) Crescentic glomerulonephritis

Focal necrotizing and crescentic glomerulonephritis frequently occur in the setting of one of the multisystem vasculitides, but may appear as a primary or idiopathic form of glomerulonephritis. However, with the introduction of reliable assays

Table III The multisystem vasculitides

<i>Multisystem disease</i>	<i>Laboratory test</i>	<i>Treatment</i>
SLE	α ds DNA Ab C3, C4	Steroids + Cycloph → Aza ⁹⁸
Microscopic polyarteritis	ANCA ¹⁰⁰	Steroids + Cycloph → Aza (± Px)
Wegener's granulomatosis	ANCA ⁹⁹	Cycloph (± Px)
Subacute bacterial endocarditis	Blood cultures + SCAT, C3, C4	Antibiotics ± IS
Henoch-Schönlein purpura	Plasma IgA IgA containing cryoglobulins	General supportive measures ± IS and Px ¹⁰⁸
Goodpasture's disease	α GBM Ab	IS + Px ¹⁰⁸
Cryoglobulinaemia	C4 + SCAT Cryocrit	Steroids + Cycloph + Px
Idiopathic (?) crescentic GN	ANCA ¹⁰⁴	Steroids + Cycloph → Aza (± Px)

Ab = Antibody; SLE = systemic lupus erythematosus; Px = Plasma exchange;
→ Change to; Cycloph = cyclophosphamide; IS = immunosuppression; Aza = azathioprine; SCAT = sheep cell agglutination titre – rheumatoid factor.

for the multisystem vasculitides such as anti-double strand DNA antibody for SLE and the ANCA antibody assay, the diagnosis of primary or idiopathic glomerulonephritis is being made less frequently.^{104,105} Clinically these lesions present either as the nephritic or nephrotic syndrome with a rapid deterioration to acute renal failure such that patients may become dialysis-dependent in a few weeks. Awareness of the rapidity of the evolution of the disease is important so that an early renal biopsy is performed.

(iii) *Henoch-Schönlein purpura (HSP)*

HSP can be a fulminating severe multisystem disorder which may be associated with the dire complication of gut vasculitis. As might be expected the patients with more than 50% of the glomeruli affected by crescents do particularly badly. Nevertheless the prognosis is generally assumed to be good particularly in children with 40% or more entering a full remission.¹¹¹ Prognosis in adults is less clear but considerably poorer with only 25% of adult patients preserving renal function.¹¹² In such patients with severe disease treatment would be along the lines suggested for microscopic polyarteritis.

(iv) *The role of plasma exchange*

As a group, whether so called 'idiopathic' or associated with a multisystem vasculitis, these conditions do respond well to immunosuppression.¹⁰⁶ The role of plasma exchange is still contro-

versial.¹⁰⁷ However, what is clear is that for the treatment of non-oliguric anti-GBM antibody-mediated disease plasma exchange remains the treatment of choice. This is particularly so in the case of lung haemorrhage irrespective of what renal function is doing. Relapses after adequate initial therapy for Goodpasture's disease are rare.^{108–110}

For non-anti-GBM antibody-mediated crescentic or focal necrotizing GN, immunosuppression with steroids and cyclophosphamide is probably sufficient. Plasma exchange, however, may be of benefit, particularly in fulminating cases and in cases in which the patients rapidly become dialysis dependent.¹⁰⁹ There are many reports of patients having been successfully treated so that renal function recovers and dialysis may be withdrawn in patients with the multisystem vasculitides. This is a rarity in Goodpasture's disease.

(v) *Lupus anticoagulant*

Arterial and venous thromboses may occur in patients with SLE or lupus-like diseases. These lesions affect many organs including the kidney, skin, heart, eyes and central nervous system. A history of recurrent spontaneous abortions is common. These clinical features are associated with the lupus anticoagulant which is an autoantibody to complex lipoprotein antigens on platelets and coagulation factors. These antibodies are responsible for the biological false positive test for syphilis (VDRL), anti-cardiolipin antibodies and the production of a prolonged PTTK. The renal lesion

associated with the lupus anticoagulant is not a glomerulonephritis as such. Vascular and intraglomerular hyaline thrombi occur. Renal veins, arterioles and glomerular capillaries may all be involved.¹¹³ Patients may present with few other features of SLE. Cortical infarcts or cortical necrosis sometimes occur.¹¹⁴ Treatment is not clearly defined but steroids plus anticoagulants or aspirin have been recommended.

Urinary tract infection

It is apparent that 30% of all women presenting with bacterial infection of the bladder have 'low colony count' bacteriuria (10^2 – 10^4 cfu/ml). The evidence for an aetiological role for such low counts in women with acute dysuria includes; isolation of *E. coli* from suprapubic aspirates, the occurrence of pyuria in 90% of cases, the association with vaginal colonization with *E. coli* in about 90% of cases, the similarity of bacterial virulence properties to those found in typical cases (i.e. those with $> 10^5$ cfu), the similarity of presentation to that in typical cases.¹¹⁵

The incidence of occult upper tract infection in patients presenting with acute cystitis, based on localization tests such as the antibody coated bacteria test or the bladder washout test, is 10–50%. The presence of occult upper tract infection has important implications for therapy.¹¹⁵

E. coli urinary tract infections in young women are usually preceded by vaginal colonization, and women with recurrent infections appear to have more frequent vaginal colonization than rarely infected women, often due to increased susceptibility of their vaginal and uroepithelial cells to adhering *E. coli*. Two host factors may be important in determining this increased susceptibility, the use of diaphragm and spermicide contraception¹¹⁵ and blood group secretor status.¹¹⁶ A number of bacterial virulence factors have been described, the most important of which are fimbrial adhesins (Gal-Gal and P), haemolysin, and aerobactin. Strains of *E. coli* with multiple virulence factors are more commonly found in upper tract infection; those in cystitis more commonly resemble faecal strains.^{115,117}

Single dose therapy for urinary tract infection particularly with amoxycillin is generally less effective than 10 day treatment, though the rates of adverse reactions are much lower. Most failures of single dose therapy manifest as early reinfection from the vaginal reservoir rather than persistent upper tract infection. This highlights the importance of the drugs effects on the vaginal flora compared with its initial effect clearing bacteriuria.¹¹⁵

Urinary isolates from patients with asymptomatic bacteriuria remain remarkably stable over the course of many years.¹¹⁸ Patients with asymptomatic bacteriuria given antibiotics (especially phenoxymethylpenicillin) for intercurrent upper respiratory tract infection frequently change bacterial strain and symptomatic urinary tract infection is often precipitated.¹¹⁹

Nephrolithiasis

The major advances in this field have been in the field of therapy. Extracorporeal shock wave lithotripsy (ESWL) has revolutionized the surgical management of the condition. Using the second generation piezo-electric devices allows stone fragmentation to be performed painlessly, without anaesthesia, as an outpatient, and with continuous ultrasound imaging.¹²⁰ Indications for its usage and its place amongst the other available treatment modalities are still undergoing revision, perhaps not surprisingly, in a field in which the pace of technological change is so rapid.

An interesting aspect of this treatment is its effect on renal function. There is little clinical data available in this area and no long term follow-up studies. Experimental work though has shown the acute effects of interstitial haemorrhage and chronic effects of interstitial fibrosis in dogs, rabbits and pigs.^{121–123} In humans increased levels of urinary enzymes were found acutely,¹²⁴ and in another study transient nephrotic range proteinuria occurred without a change in creatinine clearance. Proteinuria returned to normal within 3 to 6 months.¹²⁵

Chronic renal failure

(i) Uraemic syndrome

The quest for the uraemic toxin continues with the description of a number of new contenders^{126,127} and re-exploration of well established ones.^{128,129} A vast literature is accumulating on the role of parathyroid hormone as a uraemic toxin, much of it emanating from the originator of the concept and collaborators.¹³⁰ It is clear that parathyroid hormone is toxic (Table IV), however almost all of this data is from experimental work, much of it carried out *in vitro* and evidence for major clinically relevant effects of parathyroidectomy in uraemia other than on mineral and skeletal metabolism remains scanty.^{131–134}

(ii) Acquired cystic disease

Acquired cystic disease in end stage kidneys was described fairly recently.¹³⁵ It was originally con-

Table IV Toxic effects of parathyroid hormone

<i>Organ</i>	<i>Effect</i>
Central nervous system	EEG abnormalities ↑ brain calcium content ↓ Nad uptake and release from synaptosomes
Peripheral nerve	↓ Motor nerve conduction
Myocardium	↑ Myocardial calcium content + ve inotropic and chronotropic effect ↓ Fatty acid oxidation (↓ CPT)
Erythrocyte	↓ Erythropoiesis ↓ Erythrocyte survival (↑ osmotic fragility)
Leukocyte	↓ Random movement ↓ Elastase release ↓ T cell function
Platelet	↓ Aggregation
Skeletal muscle	↑ Amino acid release ↓ Fatty acid oxidation (↓ CPT)
Sexual function	↓ Testosterone level ↑ Calcium content of testes, pituitary, hypothalamus
Carbohydrate metabolism	↓ Insulin release from B cell ↑ Hepatic gluconeogenesis
Lipid metabolism	↓ Hepatic VLDL synthesis ↓ Peripheral metabolism of lipoproteins
Potassium metabolism	↓ Extrarenal disposition of K ⁺

Nad = noradrenaline; CPT = carnitine palmityl transferase; ↑ = increased; ↓ = decreased.

sidered to be a complication of long term haemodialysis treatment but a recent study found patient age to be the best predictor of cystic transformation and tumorous degeneration and no strong association with duration or mode of dialysis.¹³⁶ There have also been recent reports of the disease occurring in predialysis patients.^{137,138} Perhaps the most difficult clinical aspect is the management of small incidentally discovered tumours. The consensus approach seems to be annual CT monitoring for tumours of less than 3 cm, provided that they remain asymptomatic. Larger tumours, and smaller tumours occurring in symptomatic patients or in candidates for transplantation require removal. Bilateral nephrectomy is recommended in this latter group.¹³⁹

(iii) Mineral metabolism and renal bone disease

The issue of whether or not 1,25-(OH)₂D₃ has a direct suppressive effect on the parathyroid gland has long been a contentious one, but recent studies have shown definite regulatory effects of 1,25-(OH)₂D₃ on parathyroid hormone synthesis operating at the level of gene transcription.¹⁴⁰ The finding that 1,25-(OH)₂D₃ receptors in the

parathyroid gland are decreased in renal failure¹⁴¹ may also be of significance to the pathogenesis of renal bone disease. Increments in the serum level of 1,25-(OH)₂D₃ in anephric humans in response to administered 25-OHD₃ in the absence of changes in its metabolic clearance rate suggest extra-renal sites of production of 1,25-(OH)₂D₃.^{142,143} There is now good evidence that the serum concentration of phosphorus is an important physiological regulator of 1,25-(OH)₂D₃ production in normal man.¹⁴⁴ In spite of this and other accumulated data there is still uncertainty about the pathogenesis of renal bone disease especially in early renal failure. The main players are phosphorus, ionized calcium and 1,25-(OH)₂D₃ but their relative importance is unclear and different mechanisms may predominate at different stages of renal failure.¹⁴⁵

The treatment of renal bone disease also contains controversial areas. Treatment of hyperphosphataemia is a major weapon aimed at preventing hyperparathyroidism and extraskeletal calcification. Aluminium containing agents are highly effective phosphate binders¹⁴⁶ but have lately been incriminated as a major factor in the pathogenesis of aluminium toxicity. There is much recent literature centred on the search for a suitable

alternative. Dietary restriction is unnecessarily prohibitive, and dialysis techniques too inefficient, so an alternative phosphate binder is required. Calcium carbonate is the most studied.¹⁴⁷ It is effective but some patients require additional aluminium hydroxide for optimal phosphate control.¹⁴⁸ Some patients experienced mild gastrointestinal symptoms but the major side effect is hypercalcaemia carrying with it the spectre of increased extraskeletal calcification with long term use. This is a particular risk in patients taking vitamin D compounds. To offset these risks some studies have been performed in which oral calcium carbonate usage has been combined with a reduction in dialysate calcium concentration,^{149–151} with generally satisfactory results.

Reports of the phosphate binding potential of salts of heteropolyuronic acid were initially received with enthusiasm,^{152,153} but there has been very little clinical experience since,¹⁵⁴ and more data is required. Calcium citrate is undoubtedly effective but carries the risk of hypercalcaemia.¹⁵⁵ A further major risk is the potentiation of aluminium absorption which citrate undeniably causes.¹⁵⁶ Calcium acetate has recently been advocated¹⁵⁷ and use of calcium salts of ketoanalogues might kill two birds with one stone.¹⁴⁷

The other major device which has been used to control serum phosphate levels in uraemia is the combination of magnesium containing compounds which are less efficient phosphate binders than aluminium or calcium,^{146,158} and low magnesium dialysate levels to prevent toxic accumulation of magnesium. This rather cumbersome approach seems to work at least when magnesium carbonate is used.¹⁵⁸

Treatment of established hyperparathyroidism with 1 alpha-hydroxylated vitamin D compounds is well accepted and is effective at least in the short term, and prevention of established disease by treatment with low doses of these agents seems possible without the previously feared threat of accelerated progression of the underlying renal failure, provided monitoring is meticulous.¹⁵⁹ In the long term though many patients progress to develop hypercalcaemic hyperparathyroidism and treatment then becomes difficult (Figure 8). Intermittent intravenous treatment with 1,25-(OH)₂D₃ has been effective in suppressing parathyroid hormone secretion and improving bone disease without troublesome hypercalcaemia in many of these patients in whom parathyroidectomy would otherwise have been inevitable.¹⁶⁰ The reason for the superiority of the intravenous over the oral route is uncertain. Intravenous administration may cause less stimulation of intestinal calcium absorption, and may provide a more potent suppressive stimulus to the parathyroid gland by virtue of the higher plasma levels associated with intravenous

Figure 8 Management of renal osteodystrophy.

pulse administration. It has certainly been shown that the intravenous treatment increases the sensitivity of the gland to the ambient calcium level.¹⁶¹

Parathyroidectomy, however, is still frequently required, and the operation of choice is again in doubt. Over the last few years total parathyroidectomy with autotransplantation of parathyroid fragments into an accessible forearm muscle has become popular, the perceived benefit being mainly the accessibility of the grafted tissue should hypercalcaemia recur. Recently it has become clear that total parathyroidectomy is incomplete in most cases and leaves fragments of parathyroid tissue in the neck which can again become hyperplastic.^{162,163} This creates a considerable diagnostic dilemma if hypercalcaemia recurs after autotransplantation and also speaks volumes about the progressive nature of hyperparathyroidism in uraemia.

(iv) Aluminium toxicity

The accumulation within the body of uraemic patients of large amounts of aluminium is associated with severe dysfunction of many organ systems producing a severe dysplastic bone disease, disabling encephalopathy and an inappropriate anaemia. The disease was originally considered to be caused solely by aluminium accumulation from water used for dialysis but now an 'endemic' form of the disease has been identified and attributed to aluminium accumulated by ingestion of aluminium-

containing substances, particularly aluminium-containing antacids used as phosphate binders. It now appears that certain dietary substances may promote the intestinal absorption of aluminium, particularly citrate¹⁶⁴⁻¹⁶⁶ and vitamin D compounds.^{167,168}

Attention has now been directed to exploring the possible pathogenetic effects of modest accumulation of aluminium of the type seen in many dialysis patients. Aluminium removal by chelation with desferrioxamine infused during dialysis was effective in improving erythropoiesis, testifying to an inhibitory effect of modest aluminium accumulation.¹⁶⁹⁻¹⁷¹ Similar effects have also been seen on neurocognitive function¹⁷² and parathyroid hormone secretion.¹⁷³ Aluminium accumulation may also be immunosuppressive¹⁷⁴ and an independent risk factor for mortality in dialysis patients.¹⁷⁵ It has been demonstrated to inhibit cell division and protein synthesis in cell culture.¹⁷⁶

The demonstration of toxic effects at low levels of accumulation reinforces the need for precise, readily available means of diagnosis. Unfortunately serum levels both before and after desferrioxamine infusion are unreliable, correlating poorly with stainable bone stores which remains the only available means for definitive diagnosis at present.¹⁷⁷ Desferrioxamine infusion is an effective treatment but large doses may precipitate encephalopathy¹⁷⁸ and its use may be associated with an increased risk of mucormycosis, an often fatal opportunistic fungal infection.^{179,180} The aluminium desferrioxamine chelates are removed by the permeable dialysis membranes but the efficacy of removal can be increased using an activated charcoal haemoperfusion device in series with the dialyser.¹⁸¹

Finally, it has been suggested that the effective prophylaxis of aluminium toxicity by effective water treatment and restricted use of aluminium-containing phosphate binders may have unmasked another type of adynamic bone disease of unknown cause.¹⁸²

Diabetic nephropathy

Nephropathy is a major long term complication of diabetes mellitus and occurs in about 35% of patients with insulin-dependent disease. Why only this proportion of patients develop the disease is unknown. Differences in metabolic control are insufficient explanation. Familial clustering of nephropathy may suggest a hereditary susceptibility.¹⁸³ Recently it has been shown that a genetic predisposition to hypertension might increase the susceptibility of insulin-dependent diabetics to renal damage. Red cell sodium-lithium counter-transport was found to be significantly higher in

diabetics with nephropathy than in those without.^{184,185} This abnormality occurs before the onset of nephropathy¹⁸⁶ and is associated with hyperfiltration which maybe a predictor of clinical nephropathy.

The excretion of small amounts of albumin in the albugstix negative range (microalbuminuria) has been advocated as a major predictor of the development of clinical nephropathy. Improvements in metabolic control may reduce protein excretion in the microalbuminuric range but probably have no influence on the progression of nephropathy once established. Hence the advocated use of screening for microalbuminuria to identify a high risk population of diabetics upon whom the resources required to improve metabolic control could be concentrated at a time when it might be still useful. Most of this though is still conjectural. Even the definition of microalbuminuria varies between centres, its predictive value without the use of other indicators is disputed,¹⁸⁷ and its use as a screening tool is contentious.¹⁸⁸ Large scale trials, which will clarify many of these issues, are in progress but will not report for 5 years. Recommended treatment in the meantime has been outlined and involves stratification of the level of glycaemic control according to the presence or absence of microalbuminuria and early aggressive antihypertensive treatment.¹⁸⁹ Albuminuria does reflect widespread vascular damage¹⁹⁰ and microalbuminuria predicts vascular disease in non-diabetics¹⁹¹ and increased mortality in elderly patients.¹⁹²

There is no doubt that antihypertensive treatment reduces the rate of progression of established diabetic nephropathy.^{193,194} Recently it has been suggested that treatment with angiotensin converting enzyme inhibitors may confer specific benefits, making them the antihypertensive agents of choice in treating hypertension in diabetes. These agents antagonize the vasoconstrictive effects of angiotensin II on the efferent arteriole, thus lowering intraglomerular capillary as well as systemic pressures. This effect is thought to be potentially beneficial since raised intraglomerular capillary pressure may be an important determinant in the progression of renal disease.¹⁹⁵ Limited studies have so far failed to demonstrate any benefits of these agents over conventional antihypertensive treatment.¹⁹⁶ However, angiotensin converting enzyme inhibitors have been shown to prevent progression to clinical nephropathy in normotensive microalbuminuric diabetics¹⁹⁷ and prevent progressive proteinuria in normotensive diabetics with established nephropathy.¹⁹⁸

Short term protein restriction in normoalbuminuric diabetics has been shown to reduce hyperfiltration¹⁹⁹ and current theories on the mechanisms of progression of renal failure suggest

that this may be beneficial in the long term (see below). Long term protein restriction has been shown to reduce the rate of decline of creatinine clearance in established diabetic nephropathy independently of changes in blood pressure or glycaemic control.²⁰⁰ However, there may be difficulties in interpreting such data (see below). There are other modalities with possible beneficial effects including antiplatelet agents²⁰¹ and cod liver oil.²⁰² There are indications that over the last decade the prognosis of diabetic nephropathy has improved. The change has been attributed to treatment of hypertension.^{198,203}

Progression of renal failure

When renal function has deteriorated to a certain critical point then further progression to end-stage disease is inevitable, no matter what the initiating insult was, and even if it has ceased operating. The characteristic renal lesion is progressive glomerulosclerosis, associated with declining GFR, and increasing hypertension and proteinuria.

Theories to explain this sequence of events usually suggest an initiating insult causing renal damage and nephron loss, as a result of which changes occur, intrarenally or systemically, either as a direct result of the previous injury or as an adaptive response (Table V). These changes, either directly or operating through a variety of postulated amplification mechanisms cause further renal damage, thus perpetuating the process and rendering it self-sustaining.

Explanations based on the adaptive haemodynamic changes which accompany nephron loss have dominated until recently. A decade ago it was demonstrated that in many models of chronic renal failure single nephron plasma flow and GFR were elevated. It was argued that these adaptive changes to nephron loss were initially beneficial but in the long term promoted glomerulosclerosis and

accelerated the rate of decline of renal function,²⁰⁴ an effect later attributed to the associated rise in hydrostatic pressure within the glomerular capillary.²⁰⁵ The proposed mechanisms by which raised intraglomerular pressures produced these damaging effects were unclear, but included increased macromolecular traffic through the mesangium with resulting 'mesangial overload', and direct glomerular cell damage. Low protein diets and angiotensin converting enzyme inhibitors were found to protect renal function in some animal models of progressive renal failure, observations which created considerable clinical interest. However, there are an increasing number of experimental observations in which the development of glomerular sclerosis is dissociated from changes in glomerular capillary pressure,²⁰⁶ so other mechanisms must at least contribute.

Nephron loss in many situations causes an increase in glomerular size in addition to hyperperfusion and a strong correlation between the degree of glomerular hypertrophy and subsequent development of glomerulosclerosis has been noted.²⁰⁷ However, glomerular hypertrophy and glomerulosclerosis can also apparently be dissociated, particularly in situations in which severe systemic hypertension does not develop (see reference 206 for review). There is good evidence, however, that systemic hypertension accelerates the decline in renal function in many human nephropathies and experimental evidence suggests that transmission of the systemic pressure to the glomerulus by loss of autoregulation and afferent arteriolar dilatation is an important prerequisite (see reference 208 for review).

Abnormalities of lipid metabolism also occur in patients with renal disease particularly those in which there is heavy proteinuria, and it has been suggested that elevated plasma lipid levels in these situations may exacerbate renal damage.²⁰⁹ Indeed glomerulosclerosis has been likened to atherosclerosis.²¹⁰ There is some experimental evidence to support these contentions,²¹¹ but clinical evidence is lacking.

Events occurring within the tubules as a response to nephron loss have also been suggested as a possible factor leading to progression. There is a remarkable increase in oxygen consumption per nephron, mainly as a result of increased sodium reabsorption. It is postulated that this increased activity is ultimately damaging perhaps by provoking increased generation of free radicals,²¹² though there is little direct evidence for this. In summary, none of these proposed mechanisms, even the most well established, appears to operate exclusively and it appears likely that multiple factors are involved, possibly different combinations of factors will transpire to be important in different disease processes.

Only antihypertensive treatment is of proven use

Table V Renal and systemic consequences of critical nephron loss which have been proposed as mediators of progression of chronic renal disease

1.	Persistence of injured intrinsic components e.g. damage to filtration barrier resulting in persistent proteinuria.
2.	Persistence of activated infiltrating cells.
3.	Glomerular hypertrophy.
4.	Systemic hypertension.
5.	Glomerular capillary hypertension.
6.	Lipid abnormalities.
7.	Tubular hypermetabolism.

in limiting the progression of human renal diseases. Angiotensin converting enzymes offer theoretical advantages over conventional antihypertensive agents and preliminary evidence tends to support this,²¹³ but further data are required. In this context the beneficial effects of these agents (discussed above), on the progression of diabetic nephropathy which occurred in the absence of changes in blood pressure are noteworthy.^{197,198}

A large number of studies have shown apparent benefit from protein restriction. There are many pitfalls in the interpretation of such studies, particularly the adequacy of such diets to prevent nutritional deficiency,²¹⁴ assessment of compliance, the validity of serum creatinine and the reciprocal of serum creatinine in assessing the rate of progression of renal insufficiency in patients put on low protein diets,²¹⁴⁻²¹⁶ and the importance of an adequate control group.²¹⁷ Nevertheless, the results of some studies do show an impressive retarding effect on the rate of decline of renal function at least in some groups of patients,²¹⁸ though the mechanism of the effect cannot now be assumed to be solely haemodynamic, or even haemodynamic at all.

Long term haemodialysis

(i) Membrane technology

New dialysis membranes have been introduced which have defined advantages over the conventional cellulose membrane.²²⁰ These newer membranes (Table VI) are more biocompatible, cause less complement and polymorph activation than the traditional cellulosic membranes. They may be produced with an increased pore size so that the diffusive clearance of middle molecules is much enhanced. This may be of benefit in the control of the uraemic diathesis. They may also help to retard the development of dialysis arthropathy by remov-

ing or binding beta-2-microglobulin. However, these leaky membranes require more sophisticated (and therefore more expensive), dialysis machines (the so called volumetric machines). Such sophisticated machines are required to offset the very high ultra filtration rates across the more permeable membranes.

With these newer membranes it may now be both possible and safe to reduce dialysis hours to as little as 2 hours three times per week. There are, however, problems. Criteria for the adequacy of dialysis are by no means clear nor universally accepted. One criterion in wide use is the ratio KT/V where K = dialyser urea clearance, T = treatment time, V = body urea volume. Values in excess of 1 were correlated with prolonged survival and a low incidence of complications. Dialysis schedules should therefore aim to preserve KT/V .²²¹ The ultra short dialysis schedules need to be very carefully monitored and accurately tailored to each individual patient who must be precise and accurate with dialysis techniques, medical and dietary treatment. There is little margin for error. Long term studies are not available to demonstrate safety and efficacy. Short hours are of course popular with patients and have clear economic advantages for hard pressed dialysis units. In addition the newer membranes have been safely re-used many times over (as many as 30 or 40 times) which further reduces costs.

(ii) Erythropoietin

The clinical use of recombinant human erythropoietin (r-HuEPO) has transformed the lives of many anaemic dialysis patients.²²²⁻²²⁴ Many of the symptoms attributed to uraemia have resolved. Libido returns, appetite and weight increase and growth in children is improved and energy and well being are dramatically restored. The major complication that has emerged from these early studies is

Table VI Dialysis membranes

Membranes	Biocompatibility	Permeability (MW)	UFR	Uses
<i>Natural cellulosic</i>				
Cuprophane	+	1000	4-5	HD
Cellulose acetate	++	12,000	15	HD,HDF,HF
<i>Synthetic membranes</i>				
Polysulphone	+++	30,000	40	HD,HDF,HF
Polyacrylonitrile	+++	29,000	30	HD,HDF,HF
Polypropylene cellulose diacetate	++	$2-3 \times 10^9$	-	PF

HD = haemodialysis; HF = haemofiltration; HDF = haemodiafiltration; PF = plasma filtration; UFR = ultra filtration rate (ml/hour/mm/Hg); hydraulic permeability; MW = molecular weight.

that of severe hypertension which may be seen in up to one third of patients. It can be severe, difficult to treat and may be associated with seizures. The mechanism of this hypertension is not clear. It does not seem to be related to the rate of rise of haemoglobin. Factors suggested include increased blood viscosity, peripheral vasoconstriction in response to correcting tissue hypoxia and increased cardiac output. With continued use of r-HuEPO the hypertension usually becomes easier to manage. Approximately 10% of treated patients experience an increase in clotting of the extra-corporeal circulation while 15% suffer a thrombosis of vascular access.²²⁵ Itching may occur and can be intractable. Provided there are adequate iron stores therapy can be titrated to achieve a desired haemoglobin level, usually between 10 to 12 g/dl. In the grossly iron overloaded patients, erythropoietin therapy with venesection is an attractive means of clearing the excessive iron stores. Therapy is usually started at 50 U/kg thrice weekly for 4 weeks. Further increments of 25 U/kg thrice weekly may be necessary in some patients. Once the desired haemoglobin level has been reached treatment may be reduced to twice or even once weekly.

(iii) Dialysis arthropathy (amyloidosis)

Beta-2-microglobulin is a low molecular weight protein normally filtered, reabsorbed and metabolized by the kidney. It is widely distributed being a structural component of the HLA complex. In renal failure plasma levels rise in parallel with creatinine. The total daily production is between 150–200 mg per day. The consequence of a chronic elevation of beta-2-microglobulin (perhaps exacerbated by a regular thrice weekly inflammatory stimulus provided by each haemodialysis treatment) is the production and widespread deposition of amyloid material derived from beta-2-microglobulin.²²⁶ The salient clinical features are summarized in Table VII. Treatment is ineffective and

symptomatic. Attempts at prevention by the early use of the newer highly permeable biocompatible dialysis membranes may retard the process.^{227–229} Being more biocompatible these membranes reduce the inflammatory stimulus at each dialysis and some actually bind beta-2-microglobulin.²³⁰ Unfortunately the patients who have remained on dialysis for 5 to 10 years are usually also the same patients who for one reason or another cannot be transplanted which is the ideal way of avoiding this progressive and disabling complication of dialysis.

Renal transplantation

Over the last 10 years cyclosporin A has become established as the backbone of most immunosuppressive regimes and has been responsible for an improvement in graft survival of about 20%.²³¹ However, its use is plagued by nephrotoxicity and other undesirable side effects such as hirsutism, hyperuricaemia and gout²³² and gingival hyperplasia. As a consequence early news of pilot studies with a new compound, FK 506, which is five hundred times more potent than cyclosporin, yet is non-nephrotoxic, is particularly exciting. So far clinical experience is limited to Professor Starzl's unit at Pittsburgh²³³ and most of the experience in renal transplants (over 100 patients) has only been presented at meetings. FK 506 is a macrolide-(like erythromycin) and is produced by *Streptomyces tsukubaensis*. Initial use was restricted to liver transplant patients (now over 200 cases) that were either rejecting despite cyclosporin A or were in a particularly high risk group. In all the groups studied, FK 506 appeared safe, non-nephrotoxic and extremely potent. Even in high risk patients graft survivals of 90% were recorded. Clearly a formal controlled trial against cyclosporin A is eagerly awaited.

The increasing range of monoclonal antibodies is being applied to renal transplantation. So far no individual or cocktail is ideal either for the treatment of rejection or for prophylaxis. Antibodies to CD3, CD7, CD25 and CD4 have all been used with varying success.²³⁴ An exciting development in molecular biology is the ability to chimerize these molecules so that the majority of the molecule is human protein except for the antigen binding site which is murine. Preliminary studies with a chimeric human/mouse anti-CD7 antibody²³⁵ shows that these reagents are non-immunogenic, well tolerated and have immunosuppressive properties. Rapid developments are expected in this field and more reagents will be chimerized soon so that clinical experience with these remarkable molecules will enlarge rapidly.

Table VII Dialysis amyloidosis – clinical features

Carpal tunnel syndrome
Bone cysts
Pathological fractures
Joint involvement: Scapulohumeral polyarthritis
Generalized arthropathy
Effusive arthropathy
Systemic deposition: Gut
Liver
Spleen
Bladder – Ureter – Prostate

References

- Renal physiology**
- Crane, R.K. Hypothesis of mechanism of intestinal active transport of sugars. *Fed Proc* 1962, **21**: 891–895.
 - Geck, P. & Heinz, E. Secondary active transport: introductory remarks. *Kidney Int* 1989, **36**: 334–341.
 - Giebisch, G. & Boulpaep, E. (eds). Cotransport mechanisms in renal tubules. *Kidney Int* 1989, **36**: 333–440.
 - Hediger, M.A., Coady, M.J., Ieda, T.S. & Wright, E.M. Expression, cloning, and c-DNA sequencing of the Na⁺/glucose co-transporter. *Nature* 1987, **330**: 379–381.
 - Silverman, M. Molecular biology of the Na⁺-D-glucose cotransporter. *Hosp Pract* 1989, **24**: 180–204.
 - Schild, L., Giebisch, G., Karniski, L.P. & Aronson, P.S. Effect of formate on volume reabsorption in the rabbit proximal tubule. *J Clin Invest* 1987, **79**: 32–38.
 - Ellison, D.H., Velasquez, H. & Wright, F.S. Thiazide sensitive sodium chloride co-transport in early distal tubule. *Am J Physiol* 1987, **253**: F546–F554.
 - Halperin, M.L., Jungas, R.L., Cheema-Dhadli, S. & Brosnan, J.T. Disposal of daily acid load: an integrated function of the liver lungs and kidneys. *Trends Biol Sci* 1987, **12**: 197–199.
 - Atkinson, D.E. & Bourke, E. Metabolic aspects of regulation of systemic pH. *Am J Physiol* 1987, **252**: F947–F958.
 - Gluck, S.L. Cellular and molecular aspects of renal H⁺ transport. *Hosp Pract* 1989, **24**: 149–166.
 - Stone, D.K. & Xie, X.-S. Proton translocating ATPases: issues in structure and function. *Kidney Int* 1988, **33**: 167–174.
 - Halperin, M.L. How much 'new' bicarbonate is formed in the distal nephron in the presence of net acid secretion. *Kidney Int* 1989, **35**: 1277–1281.
 - Halperin, M.L., Ethier, J.H. & Kamel, S.K. Ammonium excretion in chronic metabolic acidosis: benefits and risks. *Am J Kidney Dis* 1989, **15**: 267–271.
 - Buerkert, J., Martin, D. & Trigg, D. The effect of reduced renal mass on ammonium handling and net acid formation by the superficial and juxtamedullary nephrons of the rat. *J Clin Invest* 1983, **71**: 1661–1675.
 - Nath, K.A., Hostetter, M.K. & Hostetter, T.H. Pathophysiology of chronic tubulointerstitial disease in rats. *J Clin Invest* 1985, **76**: 667–675.
 - Kelopoulos, E. Renal handling of calcium. *Am J Nephrol* 1988, **8**: 226–234.
 - Borke, J.L., Minami, J., Verma, A.K., Penniston, J.T. & Kumar, R. Co-localisation of erythrocyte Ca⁺⁺-Mg⁺⁺ ATPase and vitamin D-dependent 28-kD-calcium binding protein. *Kidney Int* 1988, **34**: 262–267.
 - Levi, M. Clinical disorders of renal tubular phosphate transport. *Am J Med Sci* 1989, **298**: 194–205.
 - Kainer, G., Spence, J.E. & Chan, J.C.M. X-linked hypophosphataemia; progress in characterisation of genetic and metabolic defects. *Nephron* 1989, **51**: 449–453.
 - Meyer, R.A. Humoral abnormalities in X-linked hypophosphataemic mice. *Nephron* 1989, **53**: 293–296.
 - Rudin, A. Bartter's syndrome. A review of 28 patients followed for 10 years. *Acta Med Scand* 1988, **224**: 165–171.
 - Garel, L., Filiatrault, D. & Robitaille, P. Nephrocalcinosis in Bartter's syndrome. *Paediatr Nephrol* 1988, **2**: 315–317.
 - Minuth, W.W., Steckelings, U. & Gross, P. Complex physiological and biochemical action of aldosterone in toad urinary bladder and mammalian collecting duct cells. *Renal Physiol* 1987, **10**: 297–310.
 - Wiedmann, P., Saxenhofer, H., Ferrier, C. & Shaw, S.G. Atrial natriuretic peptide in man. *Am J Nephrol* 1988, **8**: 1–4.
 - Buckalew, V.M. & Paschal-McCormick, C. Natriuretic hormone: current status. *Am J Nephrol* 1989, **9**: 329–342.
 - Raine, A.E.G., Firth, J.G. & Ledingham, J.G.G. The renal action of atrial natriuretic factor. *Clin Sci* 1989, **76**: 1–8.
 - Lin, S.Y., Chaves, C. & Wiedemann, E. A gamma-melanocyte-hormone-like peptide causes reflex natriuresis after acute unilateral nephrectomy. *Hypertension* 1987, **10**: 619–627.
 - Wiedmann, P., Saxenhofer, H., Ferrier, C. & Shaw, S.G. Atrial natriuretic peptide in man. *Am J Nephrol* 1988, **8**: 1–4.
 - Bell, G.M., Bernstein, R.K., Laragh, J.H. *et al.* Increased plasma atrial natriuretic factor and reduced plasma renin in patients with poorly controlled diabetes mellitus. *Clin Sci* 1989, **77**: 177–182.
 - Petersen, C., Madsen, B., Perlman, A., Chan, A.Y.M. & Myers, B.D. Atrial natriuretic peptide and the renal response to hypervolaemia in nephrotic humans. *Kidney Int* 1988, **34**: 825–831.
 - Epstein, M. Atrial natriuretic peptide in patients with liver disease. *Am J Nephrol* 1989, **9**: 89–100.
 - Windus, D.W., Stokes, T.J., Morgan, J.R. & Klahr, S. The effects of atrial peptide in humans with chronic renal failure. *Am J Kidney Dis* 1989, **13**: 477–484.
 - Wolf, A.S., Lyon, T.L., Hoffbrand, B.I., Cohen, S.L. & Moul, P.J.A. Effects of physiological infusion of atrial natriuretic factor on healthy subjects and patients with the nephrotic syndrome. *Nephron* 1989, **52**: 244–250.
 - Ferrier, C., Beretta-Piccoli, C., Wiedmann, P. *et al.* Hypotension and renal impairment during infusion of atrial natriuretic factor in liver cirrhosis with ascites. *Am J Nephrol* 1989, **9**: 291–299.
 - Shaw, G., Weidmann, P., Hodler, J., Zimmerman, A. & Paternostro, R. Atrial natriuretic factor prevents the development of acute renal failure. *J Clin Invest* 1987, **80**: 1232–1237.
 - Heibredere, E., Schaefferhans, K., Schramm, D., Gotz, R. & Heidland, A. Toxic renal failure in the rat: benefits of atrial natriuretic factor. *Klin Wschr* 1986, **64** (Suppl VI): 78–82.
 - Haberle, D.A. Haemodynamic interactions between intrinsic blood flow control mechanisms in the rat kidney. *Renal Physiol Biochem* 1988, **11**: 289–315.
 - Hirschberg, R. & Kopple, J. Increase in renal plasma flow and glomerular filtration rate during growth hormone treatment may be mediated by insulin-like growth factor I. *Am J Nephrol* 1988, **8**: 249–253.
 - Hirschberg, R. & Kopple, J.D. The effects of growth hormone and IGF-I on renal function. *Kidney Int* 1989, **36** (Suppl 27): S-20–S-26.
 - Schwertschlag, U.S., Dennis, V.W., Tucker, J.A. & Camussi, E. Nonimmunological alternations of glomerular filtration by s-PAF in the rat kidney. *Kidney Int* 1988, **34**: 779–785.
 - Kurtz, A., Schurek, H.-J., Jelkman, W. *et al.* Renal mesangium is a target for calcitonin gene-related peptide. *Kidney Int* 1989, **36**: 222–227.
 - Ofstad, J. & Iversen, B.M. The interlobular artery: its possible role in preventing and mediating renal disorders. *Nephrol Dial Transplant* 1988, **2**: 123–129.
 - Suki, W.N. Renal haemodynamic consequences of angiotensin converting enzyme inhibitors in congestive cardiac failure. *Arch Intern Med* 1989, **149**: 669–678.
- Acute renal failure**
- Butkus, D.E. Persistent high mortality in acute renal failure: are we asking the right questions? *Arch Intern Med* 1983, **143**: 209–211.
 - Cameron, J.S. Acute renal failure – the continuing challenge. *Q J Med* 1986, **59**: 337–343.
 - Turney, J.H., Marshall, D.H., Brownjohn, A.M., Ellis, C.M. & Parsons, F.M. The evolution of acute renal failure 1956–1988. *Q J Med* 1990, **74**: 83–104.
 - Church, K.S., Sakhuja, V., Malhotra, H.S. & Pereira, B.J.G. Changing trends in acute renal failure in third world countries-Chandigarh study. *Q J Med* 1989, **73**: 1117–1123.

47. Maher, E.R., Robinson, R.N., Scoble, J.E. *et al.* Prognosis of critically-ill patients with acute renal failure: APACHE II score and other predictive factors. *Q J Med* 1989, **72**: 857–866.
48. Liano, F., Garcia-Martin, F., Gallego, A. *et al.* Easy and early prognosis in acute tubular necrosis: a forward analysis of 228 cases. *Nephron* 1989, **51**: 307–313.
49. Smithies, M.N. & Cameron, J.S. Can we predict outcome in acute renal failure? *Nephron* 1989, **51**: 297–300.
50. Georgaki-Angelaki, H.N., Steed, D., Chantler, C. & Haycock, G.B. Renal function following acute renal failure in childhood: a long term follow-up study. *Kidney Int* 1989, **35**: 84–89.
51. Houghton, D.C., English, J. & Bennett, W.M. Chronic tubulointerstitial nephritis and renal insufficiency associated with long term 'subtherapeutic' gentamicin. *J Lab Clin Med* 1988, **112**: 694–703.
52. Macdougall, M.L. Aminoglycoside antibiotics: unsafe at any dose. *J. Lab Clin Med* 1988, **112**: 669–670.
53. John, J.F. What price success? The continuing saga of the toxic:therapeutic ratio in the use of aminoglycoside antibiotics. *J Infect Dis* 1988, **158**: 1–6.
54. Zager, R.A. A focus of tissue necrosis increases renal susceptibility to gentamicin administration. *Kidney Int* 1988, **33**: 84–90.
55. Parfrey, P.S., Griffiths, S.M., Barrett, B.J. *et al.* Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency or both. A prospective controlled study. *N Engl J Med* 1989, **320**: 143–149.
56. Schwab, S.J., Hlatky, M.A., Pieper, K.S. *et al.* Contrast nephrotoxicity: a randomised controlled trial of a non-ionic and an ionic radiographic contrast agent. *N Engl J Med* 1989, **320**: 149–153.
57. Schreiber, Z.A. & Dave, M.B. Acute renal failure in myeloma after ingestion of a contrast agent for cholecystography. *Nephron* 1989, **51**: 439–440.
58. Zager, R.A., O'Quigley, J., Zager, B.K. *et al.* Acute renal failure following bone marrow transplantation: a retrospective study of 272 patients. *Am J Kidney Dis* 1989, **13**: 210–216.
59. Karmali, M.A., Petric, M., Lim, C., Fleming, P.C., Arbus, G.S. & Lior, H. The association between idiopathic hemolytic-uremic syndrome and infection by verotoxin-producing *Escherichia coli*. *J Infect Dis* 1985, **151**: 775–782.
60. Aster, R.H. Plasma therapy for thrombocytopenic purpura. *N Engl J Med* 1985, **312**: 985–987.
61. Schrier, R.W., Arroyo, V., Bernardi, M., Epstein, M., Hendriksen, J.H. & Rodes, J. Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988, **8**: 1151–1157.
62. Shapiro, M.D., Nicholas, K.M., Groves, B.M. *et al.* Interrelationships between cardiac output and vascular resistance as determinants of effective arterial blood volume in cirrhotic patients. *Kidney Int* 1985, **28**: 206–211.
63. Lenz, K., Hortnagl, H., Druml, W. *et al.* Beneficial effect of 8-ornithine-vasopressin on renal dysfunction in decompensated cirrhosis. *Gut* 1989, **30**: 90–96.
64. Brezis, M., Rosen, S.N. & Epstein, F.H. The pathological influences of medullary hypoxia. *Am J Kidney Dis* 1989, **13**: 253–258.
65. McCord, J.M. Oxygen derived free radicals in post-ischaemic injury. *N Engl J Med* 1985, **312**: 159–163.
66. Canavese, C., Stratta, P. & Vercellone, A. The case for oxygen free radicals in the pathogenesis of ischaemic acute renal failure. *Nephron* 1988, **49**: 9–15.
67. Paller, M.S., Hedlund, B.E., Sikora, J.J., Faassen, A. & Waterfield, R. Role of iron in post ischaemic renal injury in the rat. *Kidney Int* 1988, **34**: 474–480.
68. Paller, M.S. & Sikora, J.J. Renal work, glutathione and susceptibility to free radical-mediated post ischaemic injury. *Kidney Int* 1988, **33**: 843–849.
69. Paganini, E.P. & Nakamoto, S. Slow continuous ultra-filtration in oliguric renal failure. *Trans Am Soc Artif Organs* 1980, **26**: 201–204.
70. Wiess, L., Danielson, B.G., Wikstrom, B., Hedstrand, U. & Wahlberg, J. Continuous arteriovenous haemofiltration in the treatment of 100 critically ill patients with acute renal failure: report on clinical outcome and nutritional aspects. *Clin Nephrol* 1989, **31**: 184–189.
71. Laver, A., Saccaggi, A., Ronco, C., Belledonne, M., Glabman, S. & Bosch, J.P. Continuous arteriovenous hemofiltration in the critically ill patient. *Ann Int Med* 1983, **99**: 455–460.
72. Schneider, N.S. & Geronemus, R.P. Continuous arteriovenous hemodialysis. *Kidney Int* 1988, **33** (S24): 159–162.
73. Tam, P.Y.-M., Huraib, S., Mahan, B. *et al.* Slow continuous haemodialysis for the management of complicated acute renal failure in an intensive care unit. *Clin Nephrol* 1988, **30**: 79–85.
74. Stevens, P.E., Riley, B., Davies, S.P. *et al.* Continuous arteriovenous haemodialysis in critically ill patients. *Lancet* 1988, **ii**: 150–152.
75. Simpson, H.K.L., Allison, M.E.M. & Telfer, A.B.M. Improving the prognosis in acute renal and respiratory failure. *Renal Failure* 1987, **10**: 45–54.
76. Heidland, A., Schafer, R.M., Heidbreder, E. & Horl, W.L. Catabolic factors in renal failure: therapeutic approach. *Nephrol Dial Transplant* 1988, **3**: 8–16.
77. Teschner, M. & Heidland, A. Hypercatabolism in acute renal failure-mechanisms and therapeutic approaches. *Blood Purif* 1989, **7**: 16–27.

Glomerulonephritis

78. Couser, W.G. & Salant, D.J. *In situ* immune complex formation and glomerular injury. *Kidney Int* 1980, **17**: 1–13.
79. Bygren, P., Cederholm, B., Heinegard, D. & Wieslander, J. Non Goodpasture anti GBM antibody in patients with glomerulonephritis. *Nephrol Dial Transplant* 1989, **4**: 254–261.
80. Humphreys, M.H. & Schoenfeld, P.Y. Renal complications in patients with the acquired immune deficiency syndrome (AIDS). *Am J Nephrol* 1987, **7**: 1–7.
81. Soni, A., Agarwal, A., Chander, P. *et al.* Evidence for an HIV-related nephropathy: a clinico-pathological study. *Clin Nephrol* 1989, **31**: 12–17.
82. Rao, T.K.S., Friedman, E.J. & Nicastri, A.D. The type of renal disease in the acquired immunodeficiency syndrome. *N Engl J Med* 1987, **316**: 1062–1068.
83. Meyrier, A. Treatment of glomerular disease with cyclosporin A. *Nephrol Dial Transplant* 1989, **4**: 923–931.
84. Williams, P.S. & Bone, J.M. Immunosuppression can arrest progressive renal failure due to idiopathic membranous glomerulonephritis. *Nephrol Dial Transplant* 1989, **4**: 181–186.
85. Ponticelli, C., Zuchelli, P., Passerini, P. *et al.* A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1989, **320**: 8–13.
86. Short, C.D., Solomon, L.R., Gokal, R. & Mallick, M.P. Methyl prednisolone in patients with membranous nephropathy and declining renal function. *Q J Med* 1987, **65**: 929–940.
87. Wehrmann, M., Bohle, A., Bogenschutz, O. *et al.* Long term prognosis of chronic idiopathic membranous glomerulonephritis. *Clin Nephrol* 1989, **31**: 67–76.
88. Nicholls, K., Fairley, K., Dowling, J. & Kincaid-Smith, P. The clinical course of mesangial IgA associated nephropathy in adults. *Q J Med* 1984, **53**: 227–250.
89. Bennett, W.M., Walker, R.G. & Kincaid-Smith, P. Treatment of IgA nephropathy with eicosapentaenoic acid (EPA): a two year prospective trial. *Clin Nephrol* 1989, **31**: 128–131.

90. Woo, K.T., Edmondson, R.P.P., Yop, H.K. *et al.* Effects of triple therapy on the progression of mesangial proliferative glomerulonephritis. *Clin Nephrol* 1987, **27**: 56–64.
 91. Waldo, F.B., Alexander, R., Wyatt, R.J. & Kohaut, E.C. Alternate day prednisolone in children with IgA associated nephritis. *Am J Kidney Dis* 1989, **13**: 55–60.
 92. Kobayashi, Y., Fujii, K., Hiki, Y. *et al.* Steroid therapy in IgA nephropathy: a prospective pilot study in moderate proteinuric cases. *Q J Med* 1986, **61**: 935–943.
 93. Donadio, J.V. & Offord, K.P. Reassessment of treatment results in membranoproliferative glomerulonephritis, with emphasis on life-table analysis. *Am J Kidney Dis* 1989, **14**: 445–451.
 94. Kasiske, B.L., Velosa, J.A., Halstenson, C.E., La Belle, P., Legendorfer, A. & Keane, W.F. The effects of lovastatin in hyperlipidaemic patients with the nephrotic syndrome. *Am J Kidney Dis* 1990, **15**: 8–15.
 95. Kaysen, G.A., Gambertoglio, J., Jimenez, I., Jones, H. & Hutchinson, F.N. Effects of dietary protein intake on albumin homeostasis in nephrotic patients. *Kidney Int* 1986, **29**: 572–577.
 96. Anderson, S., Rennke, H.G. & Brenner, B.M. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension. *J Clin Invest* 1986, **77**: 1993–2000.
- Multisystem vasculitides**
97. Felson, D.J. & Anderson, J. Evidence for the superiority of immunosuppressive drugs and prednisolone alone in lupus nephritis: results of a pooled analysis. *N Engl J Med* 1984, **311**: 1528–1533.
 98. Austin, H.A., Klippel, J.H., Barlow, J.E. *et al.* Therapy of lupus nephritis: controlled trial of prednisolone and cytotoxic drugs. *N Engl J Med* 1986, **514**: 614–619.
 99. Van der Woude, F.J., Rasmussen, N., Lobatto, S. *et al.* Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985, **ii**: 425–429.
 100. Savage, C.O.S., Winearls, C.G., Jones, S., Marshall, P.D. & Lockwood, C.M. Prospective study of radioimmunoassay for antibodies against neutrophil cytoplasm in the diagnosis of systemic vasculitis. *Lancet* 1987, **i**: 1389–1393.
 - 100a. Leaker, B. & Cambridge, G. Anti-neutrophil cytoplasmic antibodies and vasculitis. *Postgrad Med J* 1990, **66**: 77–79.
 101. Abbott, F., Jones, S., Lockwood, C.M. & Rees, A.J. Autoantibodies to glomerular antigens in patients with Wegener's granulomatosis. *Nephrol Dial Transplant* 1989, **4**: 1–8.
 102. Keller, F., Oehlenberg, B., Kunzendorf, U., Schwartz, A. & Offerman, G. Long term treatment and prognosis of rapidly progressive glomerulonephritis. *Clin Nephrol* 1989, **41**: 190–197.
 103. Baldwin, D.S., Neugarten, J., Feiner, H.D., Gluck, M. & Spinowitz, B. The existence of a protracted course in crescentic glomerulonephritis. *Kidney Int* 1987, **31**: 790–794.
 104. Falk, R.J. & Jennette, J.C. Antineutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 1988, **318**: 1651–1657.
 105. Pusey, C.D. & Lockwood, C.M. Autoimmunity in rapidly progressive glomerulonephritis. *Kidney Int* 1989, **35**: 929–937.
 106. Couser, W.G. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms and therapy. *Am J Kidney Dis* 1988, **11**: 449–464.
 107. Glöckner, W.M., Sieberth, H.G., Wichmann, H.E. *et al.* Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis. A controlled multicentre study. *Clin Nephrol* 1988, **29**: 1–8.
 108. Savage, C.O.S., Pusey, C.D., Bowman, C., Rees, A.J. & Lockwood, C.M. Antiglomerular basement membrane antibody mediated disease in the British Isles. 1980–1984. *Br Med J* 1986, **292**: 301–304.
 109. Pusey, C.D. & Lockwood, C.M. Plasma exchange for glomerular disease. In: Robinson, P.R. (ed.) *Nephrology*. Springer Verlag, New York, 1984, pp. 1474–1485.
 110. Johnson, J.P., Moore, J., Austin, H.A., Balow, J.E., Antonovych, T.T. & Wilson, C.C. Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathological and treatment factors. *Medicine* 1985, **64**: 219–227.
 111. Counahan, R., Winterborn, M.H., White, R.H.R. *et al.* Prognosis of Henoch-Schönlein nephritis in children. *Br Med J* 1977, **2**: 11–14.
 112. Fogazzi, G.B., Pasquali, S., Moriggi, M. *et al.* Long term outcome of Schönlein-Henoch nephritis in the adult. *Clin Nephrol* 1989, **31**: 60–66.
 113. Kincaid-Smith, P., Fairley, K.F. & Kloss, M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy related renal failure. *Q J Med* 1988, **69**: 795–815.
 114. Kleinknecht, D., Bobbie, G., Meyer, O., Noel, L.H., Callard, P. & Ramdane, M. Recurrent thrombosis and renal vascular disease in patients with lupus anticoagulant. *Nephrol Dial Transplant* 1989, **4**: 854–858.
- Urinary tract infection**
115. Stamm, W.E., Hooton, T.M., Johnson, J.R. *et al.* Urinary tract infection: from pathogenesis to treatment. *J Infect Dis* 1989, **159**: 400–406.
 116. Sheinfeld, J., Schaeffer, A.J., Cordon-Cardo, C., Rogatko, A. & Fair, W.R. Association of the Lewis blood group type with recurrent urinary tract infection in women. *N Engl J Med* 1989, **320**: 773–777.
 117. Schoolnik, G.K. How *Escherichia coli* infects the urinary tract. *N Engl J Med* 1989, **320**: 804–805.
 118. Hansson, S., Caugert, D., Jodal, U. & Svanborg-Edin, C. Untreated asymptomatic bacteriuria in girls: stability of urinary isolates. *Br Med J* 1989, **298**: 853–855.
 119. Hansson, S., Jodal, U., Lincoln, K. & Svanborg-Edin, C. Untreated asymptomatic bacteriuria in girls: effect of phenoxymethylpenicillin and erythromycin given for intercurrent infection. *Br Med J* 1989, **298**: 856–859.
- Nephrolithiasis**
120. Bowsher, W.G., Carter, S., Philp, T. *et al.* Clinical experience using the Wolf piezolith device at 2 British stone centres. *J Urol* 1989, **142**: 679–682.
 121. Abrahams, C., Lipson, S. & Ross, L. Pathologic changes in the kidneys and other organs of dogs undergoing extracorporeal shockwave lithotripsy with a tubeless lithotripter. *J Urol* 1988, **140**: 391–394.
 122. Gunasekaran, S., Donovan, J.M., Chvapil, M. & Drach, G.W. Effects of extracorporeal shockwave lithotripsy on the structure and function of rabbit kidney. *J Urol* 1989, **141**: 1250–1254.
 123. Begun, K.P., Lawson, R.K., Kearns, C.M. & Tieu, T.M. Electrohydraulic shock wave induced renal injury. *J Urol* 1989, **142**: 155–159.
 124. Assimios, D.G., Boyce, W.H., Furr, E.G. *et al.* Selective elevation of urinary enzyme levels after extracorporeal shockwave lithotripsy. *J Urol* 1989, **142**: 687–690.
 125. Gilbert, B.R., Riehle, R.A. & Vaughan, E.D. Extracorporeal shockwave lithotripsy and its effects on renal function. *J Urol* 1988, **139**: 482–485.
- Chronic renal failure**
126. Mabuchi, H. & Nakahashi, H. A major endogenous ligand substance involved in renal failure. *Nephron* 1988, **49**: 227–280.

127. Yanagisawa, H. & Wada, O. Significant increase of IQ-type heterocyclic amines, dietary carcinogens in the plasma of patients with uraemia just before induction of haemodialysis treatment. *Nephron* 1989, **52**: 6–10.
128. Nathan, I., Hensel, R., Dvilansky, A. & Shainken-Kestenbaum, R. Effect of uraemic toxins-Guanidino compounds and creatinine- on proliferation of HL60 and H562 cell lines. *Nephron* 1989, **52**: 251–252.
129. Yokozawa, T., Mo, Z.L. & Oura, H. Comparison of toxic effects of methylguanidine, guanidinosuccinic acid, and creatinine in rats with adenine-induced chronic renal failure. *Nephron* 1989, **51**: 388–392.
130. Massry, S.G. Is parathyroid hormone a uraemic toxin? *Nephron* 1977, **19**: 125.
131. Drueke, T., Fleury, I., Toure, Y. *et al.* Effect of parathyroidectomy on left ventricular ejection fraction in haemodialysis patients. *Lancet* 1980, **i**: 112.
132. Zuchelli, P., Santoro, A., Zuchelli, A., Spongano, M. & Ferrari, G. Long term effects of parathyroidectomy on cardiac and nervous system functions in haemodialysis patients. *Nephrol Dial Transplant* 1988, **3**: 45–50.
133. Potasman, I. & Better, O.S. The role of secondary hyperparathyroidism in the anaemia of chronic renal failure. *Nephron* 1983, **33**: 229.
134. Cassidy, M.J.D., Ellis, H.A. & Dewar, J. The anaemia of chronic renal failure: is there an association with hyperparathyroidism? *Kidney Int* 1984, **26**: 897.
135. Dunnill, M.S., Millard, P.R. & Oliver, D. Acquired cystic disease of the kidneys: a hazard of long term intermittent maintenance haemodialysis. *J Clin Pathol* 1977, **30**: 868–877.
136. Miller, L.R., Soffer, O., Nassar, V.H. & Kutner, M.H. Acquired cystic disease in end-stage renal disease: an autopsy study of 155 cases. *Am J Nephrol* 1989, **9**: 322–328.
137. Lindquist, B., Wahlin, A., Lundstrom, B. *et al.* Non familial polycystic kidney without enlargement. *Nephron* 1985, **39**: 134.
138. Chung-Park, M., Parveen, T. & Lam, M. Acquired cystic disease of the kidneys and renal cell carcinoma in chronic renal insufficiency without dialysis treatment. *Nephron* 1989, **53**: 157–161.
139. Grantham, J.J. & Gabow, P.A. Polycystic kidney disease. In: Schrier, R.W. & Gottschalk, C.W. (eds). *Diseases of the Kidney*. Little, Brown, Boston, Toronto, 1988, 583–615.
140. Russell, J., Letteri, D. & Sherwood, L.M. Suppression by 1,25(OH)₂D₃ of transcription of the parathyroid hormone gene. *Endocrinology* 1986, **119**: 2864–2866.
141. Brown, A.J., Dusso, A., Lopez-Hilker, S., Lewis-French, J., Grooms, P. & Slatopolsky, E. 1,25(OH)₂D₃ receptors are decreased in parathyroid glands from clinically uraemic dogs. *Kidney Int* 1989, **35**: 19–23.
142. Dusso, A., Lopez-Hilker, S., Rapp, N. & Slatopolsky, E. Extrarenal production of calcitriol in chronic renal failure. *Kidney Int* 1988, **34**: 368–375.
143. Dusso, A., Lopez-Hilker, S., Lewis-French, J., Grooms, P., Brown, A., Martin, K. & Slatopolsky, E. Metabolic clearance rate and production of calcitriol in uraemia. *Kidney Int* 1989, **35**: 860–864.
144. Portale, A.A., Halloran, B.D. & Morris, R.C. Jr. Physiological regulation of serum concentration of 1,25-dihydroxyvitamin D by phosphorous in normal man. *J Clin Invest* 1989, **83**: 1495–1499.
145. Feinfeld, D.A. & Sherwood, L.M. Parathyroid hormone and 1,25(OH)₂D₃ in chronic renal failure. *Kidney Int* 1988, **33**: 1049–1058.
146. Sheikh, M.S., Maguire, J.A., Emmett, M. *et al.* Reduction of dietary phosphorous absorption by phosphate binders. *J Clin Invest* 1989, **83**: 66–73.
147. Schaeffer, K., Early, C.M., von Herrath, D. & Stein, G. Calcium salts of ketoacids as a new treatment strategy for uraemic hyperphosphataemia. *Kidney Int* 1989, **36** (Suppl 27): S136–S139.
148. Slatopolsky, E., Weerts, C., Lopez-Hilker, S. *et al.* Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 1986, **315**: 157–161.
149. Slatopolsky, E., Weerts, C., Norwood, K. *et al.* Long term effects of calcium carbonate and 2.5 m Eq/liter calcium dialysate on mineral metabolism. *Kidney Int* 1989, **36**: 897–903.
150. Mactier, R.A., Van Stone, A.J., Van Stone, M.C. & Twardowski, Z. Calcium carbonate is an effective phosphate binder when the dialysate calcium concentration is adjusted to control hypercalcaemia. *Clin Nephrol* 1987, **28**: 222–226.
151. Sawyer, N., Noonan, K., Altmann, P., Marsh, F. & Cunningham, J. High dose calcium carbonate with stepwise reduction in dialysate calcium concentrations: effective phosphate control and aluminium avoidance in haemodialysis patients. *Nephrol Dial Transplant* 1989, **4**: 105–109.
152. Schneider, H., Kulbe, K.D., Weber, H. & Streicher, E. High-effective aluminium-free phosphate binder. *In vitro* and *in vivo* studies. *Proc Eur Dial Transplant Assoc* 1983, **20**: 725–729.
153. Schneider, H.W., Kulbe, K.D., Weber, H. & Streicher, E. *In vitro* and *in vivo* studies with a non aluminium phosphate binding compound. *Kidney Int* 1986, **29** (Suppl 18): S120–S123.
154. Passlick, J., Wilhelm, M., Busch, T.H. & Ohnesorge, F.K. Calcium alginate, an aluminium-free phosphate binder in patients on CAPD. *Clin Nephrol* 1989, **32**: 96–100.
155. Cushner, H.M., Copley, J.B., Lindberg, J.S. & Foulkes, C.J. Calcium citrate, a nonaluminium-containing phosphate binding agent for treatment of CRF. *Kidney Int* 1988, **33**: 95–99.
156. Molitoris, B.A., Froment, D.H., Mackenzie, T.A., Huffer, W.H. & Alfrey, A.C. Citrate: a major factor in the toxicity of orally administered aluminium compounds. *Kidney Int* 1989, **36**: 949–953.
157. Schiller, L.R., Santa Ana, C.A., Sheikh, M.S., Emmett, M. & Fordtran, J.S. The effect of the time of administration of calcium acetate on phosphorous binding. *N Engl J Med* 1989, **320**: 1110–1113.
158. O'Donovan, R., Baldwin, D., Hammer, M., Moniz, C. & Parsons, V. Substitution of aluminium salts by magnesium salts in control of hyperphosphataemia. *Lancet* 1986, **i**: 880–882.
159. Baker, L.R.I., Abrams, S.M.A., Roe, C.J., Faugere, P.L., Subayti, Y. & Malluche, H.H. 1,25(OH)₂D₃ administration in moderate renal failure: a prospective double-blind trial. *Kidney Int* 1989, **35**: 661–669.
160. Andress, D.L., Norris, K.C., Coburn, J.W., Slatopolsky, E.A. & Sherrard, D.J. Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med* 1989, **321**: 274–279.
161. Delmez, J.A., Tindira, C., Grooms, P., Dusso, A., Windus, D.W. & Slatopolsky, E. Parathyroid hormone suppression by intravenous 1,25-dihydroxyvitamin D. A role for increased sensitivity to calcium. *J Clin Invest* 1989, **83**: 1349–1355.
162. Farrington, K., Varghese, Z., Chan, M.K. *et al.* How complete is a total parathyroidectomy in uraemia? *Br Med J* 1987, **294**: 743.
163. Kaye, M., D'Amour, P.D. & Henderson, J. Elective total parathyroidectomy without autotransplantation in end stage renal disease. *Kidney Int* 1989, **35**: 1390–1399.
164. Molitoris, B.A., Froment, D.H., Mackenzie, T.A., Huffer, W.H. & Alfrey, A.C. Citrate: a major factor in the toxicity of orally administered aluminium compounds. *Kidney Int* 1989, **36**: 949–953.
165. Froment, D.P., Molitoris, B.A., Buddington, B., Miller, N. & Alfrey, A.C. Site and mechanism of enhanced gastrointestinal absorption of aluminium by citrate. *Kidney Int* 1989, **36**: 978–984.

166. Kirschbaum, B.B. & Schoolwerth, A.C. Acute aluminium toxicity associated with oral citrate and aluminium containing antacids. *Am J Med Sci* 1989, **297**: 9–11.
167. Ittel, T.H., Kluge, R. & Sieberth, H.G. Enhanced gastrointestinal absorption of aluminium in uraemia: time course and effect of vitamin D. *Nephrol Dial Transplant* 1988, **3**: 617–623.
168. Demonitis, R., Reissi, D., Noel, C. *et al.* Indirect clinical evidence that 1- α -OH vitamin D increases the intestinal absorption of aluminium. *Clin Nephrol* 1989, **31**: 123–127.
169. Altmann, P., Plowman, D., Marsh, E. & Cunningham, J. Aluminium chelation therapy in dialysis patients; evidence for inhibition of haemoglobin synthesis by low levels of aluminium. *Lancet* 1988, **i**: 1012–1015.
170. De la Serna, F.J., Praga, M., Gilsantz, F., Rodicio, J.-L., Ruilope, L.-M. & Alcazar, J.-M. Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. *Lancet* 1988, **i**: 1009–1011.
171. Bia, M.J., Cooper, K., Schnall, S. *et al.* Aluminium induced anaemia: pathogenesis and treatment in patients on chronic haemodialysis. *Kidney Int* 1989, **36**: 852–858.
172. Sprague, S.M., Corwin, H.L., Tanner, C.M., Wilson, R.S., Green, B.J. & Goetz, C.G. Relationship of aluminium to neurocognitive function in chronic dialysis patients. *Arch Intern Med* 1988, **148**: 2169–2172.
173. Felsenfeld, A.J., Rodriguez, M., Coleman, M., Ross, D. & Llach, F. Desferrioxamine therapy in haemodialysis patients with aluminium associated bone disease. *Kidney Int* 1989, **35**: 1371–1378.
174. Nordal, K.P., Dahl, E., Albrechtsen, D. *et al.* Aluminium accumulation and immunosuppressive effect in recipients of kidney transplantation. *Br Med J* 1988, **297**: 1581–1583.
175. Chazan, J.A., Blonsky, S.L., Abuelo, J.G. & Pezzula, J.C. Increased body aluminium. An independent risk factor in patients undergoing long-term haemodialysis. *Arch Intern Med* 1988, **148**: 1817–1820.
176. Blair, H.C., Finch, J.L., Avioli, R., Crouch, E.C., Slatopolsky, E. & Teitelbaum, S.L. Micromolar aluminium levels reduce ^3H -thymidine incorporation by cell line UMR 106-01. *Kidney Int* 1989, **35**: 1119–1125.
177. Malluche, H.H. & Faugere, M.-L. Aluminium related bone disease. *Blood Purif* 1988, **6**: 1–15.
178. Sherrard, D.J., Walker, J.V. & Boykin, J.L. Precipitation of dialysis dementia by desferrioxamine treatment of aluminium related bone disease. *Am J Kidney Dis* 1988, **12**: 126–130.
179. Daly, A.L.D., Velasquez, L.A., Bradley, S.F. & Kauffman, K.A. Mucormycosis: association with desferrioxamine therapy. *Am J Med* 1989, **87**: 458–471.
180. Eiser, A.R., Scifkin, R.F. & Neff, M.S. Intestinal mucormycosis in hemodialysis patients following desferrioxamine. *Am J Kidney Diseases* 1987, **10**: 71–73.
181. Delmez, J., Weerts, C., Lewis-Finch, J., Windus, D. & Slatopolski, E. Accelerated removal of desferrioxamine – mesylate – chelated aluminium by charcoal hemoperfusion in hemodialysis patients. *Am J Kidney Diseases* 1989, **13**: 308–311.
182. Moriniere, P., Cohen-Solal, M., Belbrick, S. *et al.* Disappearance of aluminic bone disease in a long term asymptomatic dialysis population restricting $\text{Al}(\text{OH})_3$ intake: Emergence of adynamic bone disease not related to aluminium. *Nephron* 1989, **53**: 93–101.
- Diabetic nephropathy**
183. Seaquist, E.R., Goetz, F.C., Rich, S. & Barbosa, J. Familial clustering of diabetic kidney disease. Evidence for a genetic susceptibility to diabetic nephropathy. *N Engl J Med* 1989, **320**: 1161–1165.
184. Mangili, R., Bending, J.J., Scott, G., Gupta, A. & Viberti, G. Increased sodium-lithium countertransport in red cells of patients with insulin dependent diabetes and nephropathy. *N Engl J Med* 1988, **318**: 146–150.
185. Krolewski, A.S., Canessa, M., Warram, J.H. *et al.* Predisposition to hypertension susceptibility to renal disease in insulin dependent diabetes mellitus. *N Engl J Med* 1988, **318**: 140–145.
186. Carr, S., Mbanya, J.-C., Thomas, T. *et al.* Increase in glomerular filtration rate in patients with insulin dependent diabetes and elevated erythrocyte sodium-lithium countertransport. *N Engl J Med* 1990, **322**: 500–505.
187. Chavers, B.M., Bilous, R.W., Ellis, E.N., Steffes, M.W. & Mauer, S.M. Glomerular lesions and urinary albumin excretion in type 1 diabetes without overt proteinuria. *N Engl J Med* 1989, **320**: 966–969.
188. Bennett, P.H. Microalbuminuria and diabetes. A critique-assessment of urinary albumin excretion and its role in screening for diabetic nephropathy. *Am J Kidney Dis* 1989, **13**: 29–34.
189. Mogensen, C.E. Long term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J* 1982, **285**: 685–688.
190. Deckert, T., Feldt-Rasmussen, B., Bord-Johnsen, K., Jensen, T. & Kofeod-Eneuddsen, A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989, **32**: 219–226.
191. Yudkin, J.S., Forrest, R.D. & Jackson, C.A. Microalbuminuria as a predictor of vascular disease in non-diabetic subjects. *Lancet* 1988, **ii**: 530.
192. Damsgaard, E.M., Frohland, A., Jorgensen, O.D. & Mogensen, C.E. Microalbuminuria: a predictor of increased mortality in elderly people. *Br Med J* 1990, **300**: 297–300.
193. Mogensen, C.E. Management of diabetic renal involvement and disease. *Lancet* 1988, **i**: 867–870.
194. Parving, H.H., Anderson, A.R., Smidt, U.M. & Svedsen, P.A. Early aggressive antihypertensive treatment reduces the rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983, **i**: 1175–1179.
195. Anderson, S., Meyer, T.W., Rennke, H.G. & Brenner, B.M. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1985, **76**: 612–619.
196. Baba, T., Murabayashi, S. & Takebe, K. Comparison of the renal effects of angiotensin converting enzyme inhibitor and calcium antagonist in hypertensive Type 2 (non-insulin-dependent) diabetic patients with microalbuminuria: a randomised controlled trial. *Diabetologia* 1989, **32**: 40–44.
197. Marre, M., Chatelier, G., Leblanc, H., Guyene, T.T., Menard, J. & Passa, P. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *Br Med J* 1988, **297**: 1092–1095.
198. Parving, H.H., Hommel, E., Damkjaer, M.D. & Giese, J. Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *Br Med J* 1989, **299**: 533–537.
199. Mau Pedersen, M., Mogensen, C.E., Schonau Jorgensen, F., Moller, B., Lykke, G. & Pedersen, O. Renal effects from limitation of high dietary protein in normoalbuminuric diabetic patients. *Kidney Int* 1989, **27**: S115–S121.
200. Walker, J.D., Bending, J.J., Dods, R.A. *et al.* Restriction of dietary protein and progression of renal failure in diabetic nephropathy. *Lancet* 1989, **ii**: 1411–1414.
201. Hopper, A.H., Tindall, H. & Davies, J.A. Administration of Aspirin-Dipyridamole reduces proteinuria in diabetic nephropathy. *Nephrol Dial Transplant* 1989, **4**: 140–143.
202. Jensen, T., Stender, S., Goldstein, K., Holmer, G., Deckert, T. Partial normalisation by dietary cod liver oil of increased microvascular albumin leakage in patients with insulin dependent diabetes and albuminuria. *N Engl J Med* 1989, **321**: 1572–1577.
203. Mathiesen, E.R., Borch-Johnsen, K., Jensen, D.V. & Deckert, T. Improved survival in patients with diabetic nephropathy. *Diabetologia* 1989, **32**: 884–886.

Progress of renal failure

204. Hostetter, T.H., Olsen, J.L., Rennke, H.G. *et al.* Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981, **241**: F85–F93.
205. Anderson, S., Meyer, T.W., Rennke, H.G. & Brenner, B.M. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1985, **76**: 612–619.
206. El Nahas, A.M. Glomerulosclerosis: insights into pathogenesis and treatment. *Nephrol Dial Transplant* 1989, **4**: 843–853.
207. Yoshida, Y., Fogo, A. & Ichikawa, T. Glomerular haemodynamic changes versus hypertrophy in experimental glomerular sclerosis. *Kidney Int* 1989, **35**: 654–660.
208. Baldwin, D.S. & Neugarten, J. Blood pressure control and progression of renal insufficiency. *Contemporary Issues in Nephrology* 1986, **14**: 81–110.
209. Moorhead, J.F., Chan, M.K., El Nahas, M. & Varghese, Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulointerstitial disease. *Lancet* 1982, **i**: 1309–1312.
210. El Nahas, A.M. Glomerulosclerosis: a form of atherosclerosis. *Proceedings of the Xth International Congress of Nephrology* 1987, **ii**: 1206–1220.
211. Keane, W.F., Kasiske, B.L. & O'Donnell, M.P. Lipids and progressive glomerulosclerosis. *Am J Nephrol* 1988, **8**: 261–271.
212. Schrier, R.W., Harris, D.C.H., Chan, L., Shapiro, J. & Caramelo, C. Tubular hypermetabolism as a factor in the progression of chronic renal failure. *Am J Kidney Dis* 1988, **12**: 243–249.
213. Mann, J. & Ritz, E. Preservation of renal function by use of converting enzyme inhibitors for control of hypertension. *Lancet* 1987, **ii**: 619–622.
214. Druml, W. & Mitch, W.E. Protein restricted diet and the progression of renal failure. *Blood Purif* 1988, **6**: 285–298.
215. El Nahas, A.M. & Coles, G.A. Dietary treatment of chronic renal failure: ten unanswered questions. *Lancet* 1986, **i**: 597–600.
216. Walser, M., Drew, H.H. & Lafrance, N.D. Creatinine measurements often yield false estimates of progression in chronic renal failure. *Kidney Int* 1988, **34**: 412–418.
217. Bergstrom, J., Alvestrand, A., Bucht, H. & Gutierrez, A. What is the role of controls in an outpatient department of progression of renal disease? *Blood Purif* 1988, **6**: 336–342.
218. Rosman, J.B., Langer, K., Brandl, M. *et al.* Protein restricted diets in chronic renal failure: a 4 year follow-up shows limited indications. *Kidney Int* 1989, **36** (Suppl 27): S96–S102.
219. Ihle, B.U., Becker, G.T., Whitworth, J.A., Charlwood, R.A. & Kincaid-Smith, P.S. The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 1989, **321**: 1774–1777.
221. Gotch, F.A. & Sargent, J.A. A mechanistic analysis of the national cooperative dialysis study (NCDS). *Kidney Int* 1985, **28**: 526–534.
222. Winnearls, C.G., Oliver, D.O., Reid, C., Downing, M.R., Pippard, M.R. & Cotes, P.M. Effects of human erythropoietin derived from recombinant DNA in the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986, **ii**: 1175–1177.
223. Winnearls, C.G. Erythropoietin. *Nephrol Dial Transplant* 1989, **4**: 323–326.
224. Eshbach, J.W., Egrie, J.C., Downing, M.R., Browne, J.K. & Adamson, J.W. Correction of the anaemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and phase II clinical trial. *N Engl J Med* 1987, **316**: 73–78.
225. Sundal, E. & Kaeser, V. Correction of anaemia of chronic renal failure with recombinant human erythropoietin: safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis dependent patients. *Nephrol Dial Transplant* 1989, **4**: 979–987.
226. Kleinman, K.S. & Coburn J.W. Amyloid syndromes associated with haemodialysis. *Kidney Int* 1989, **35**: 567–575.
227. Takeyama, T., Kunitomo, T., Kobayashi, T. *et al.* Development of the dialysers for B2 microglobulin removal. *Kidney Dialysis* 1987, **23**(S): 118–120.
228. Floege, J., Granolleras, C., Deschodt, G. *et al.* High flux synthetic versus cellulose membranes for B2 microglobulin removal during hemodialysis, hemodiafiltration and hemofiltration. *Nephrol Dial Transplant* 1989, **4**: 653–657.
229. Akizawa, T., Koshikawa, S., Nahazawa, R., Yoshida, T., Kaneko, M. & Nitadori, Y. Elimination of B2 microglobulin by a new polyacrylonitrile membrane dialyser: mechanism and physiokinetics. *Nephrol Dial Transplant* 1989, **4**: 356–365.
230. Ono, T., Iwamoto, N., Kataoka, H. *et al.* Clinical significance of a dialysis membrane that can remove B2 microglobulin. *Trans Am Soc Artif Intern Organs* 1988, **34**: 342–345.

Renal transplantation

231. Kahan, B.D. Cyclosporin A. *N Engl J Med* 1989, **321**: 1725–1738.
232. Lin, H.-Y., Rocher, L.L., McQuillan, M.A., Schmaltz, S., Palella, T.D. & Fox, I.H. Cyclosporin induced hyperuricaemia and gout. *N Engl J Med* 1989, **321**: 287–292.
233. Starzl, T.E., Fung, J., Venkatarammah, R., Todo, S., Demetris, A.J. & Jain, A. FK506 for liver, kidney and pancreas transplantation. *Lancet* 1989, **ii**: 1000–1004.
234. Carpenter, C.B., Suthanthiran, M. (eds). The prophylactic use of monoclonal antibodies in renal transplantation. *Am J Kidney Dis* 1989, **14** (Suppl 2): 1–77.
235. Sweny, P., Amlot, P., Fernando, O. *et al.* Pilot study of a chimeric human/mouse CD7 monoclonal antibody (SDZ CHH380) in renal transplantation. International Transplantation Society Meeting, 1990.

Long term haemodialysis

220. Mujais, S. & Ivanovich, P. Membranes for extracorporeal therapy. In: Maher, J.F. (ed.). *Replacement of Renal Function by Dialysis*, 3rd Edition. Kluwer Academic Publishers, Dordrecht, 1989, pp. 181–188.