21.9.2 Chronic tubulointerstitial nephritis 4956 M

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section 21 Disorders of the kidney and urinary tract 4956 González E, et al. (2008). Early steroid treatment improves the re- covery of renal function in patients with drug-induced acute inter- stitial nephritis. Kidney Int, 73, 940–6. Quinto LR, Sukkar L, Gallagher M (2019). Effectiveness of cortico- steroid compared with non-corticosteroid therapy for the treatment of drug-induced acute interstitial nephritis: a systematic review. Intern Med J, 49, 562–9. Raghavan R, Eknoyan G (2014). Acute interstitial nephritis—a re- appraisal and update. Clin Nephrol, 82, 149–62. Randhawa P, Brennan DC (2006). BK virus infection in transplant re- cipients: an overview and update. Am J

Transplant, 6, 2000–5. Rossert J (2001). Drug-induced acute interstitial nephritis. Kidney Int, 60, 804–17. Ruffing KA, et al. (1994). Eosinophils in urine revisited. Clin Nephrol, 41, 163–6. 21.9.2 Chronic tubulointerstitial nephritis Marc E. De Broe, Channa Yamasumana, Patrick C. D'Haese, Monique M. Elseviers, and Benjamin Vervaet ESSENTIALS Chronic tubulointerstitial nephritis is usually asymptomatic, presenting with slowly progressive renal impairment. Urinalysis may be normal or show low-grade proteinuria (<1.5 g/day) and/or pyuria. Diagnosis depends on renal biopsy, which reveals variable cellular infiltration of the interstitium, tubular atrophy, and fibrosis. There are many causes including sarcoidosis, drugs (prescribed and nonprescribed), irradi- ation, toxins, and metabolic disorders. Analgesic nephropathy—this is characterized by renal papillary necrosis and chronic interstitial nephritis and is caused by the pro- longed and excessive consumption of combinations of analgesics, mostly including phenacetin. In the 1960s and 1970s, this was the cause of endstage renal failure in up to 20% of patients on dialysis in some countries (including Australia and Belgium), but it is now a rare condition following withdrawal of phenacetin and limitations in the over-the-counter availability of compound analgesic mixtures in most countries. It is associated with a high incidence of urothelial malignancy. Nonsteroidal anti-inflammatory drugs—the most frequent cause of permanent renal insufficiency after acute interstitial nephritis, risk factors for irreversible failure being pre-existing renal damage, long- standing intake of the causative drug, slow oligosymptomatic disease development, and histological signs of chronicity. Aristolochic acid nephropathy—Chinese herb nephropathy—first recognized in women presenting with renal failure, often near endstage, following exposure to a slimming regimen containing Chinese herbs. Renal biopsy reveals extensive interstitial fibrosis with atrophy and loss of the tubules, but with little cellular infiltration. It is caused in most cases by aristolochic acid, and is associated with a high incidence of urothelial malignancy. Aristolochic acid nephropathy—Balkan endemic nephropathy—a chronic, familial, noninflammatory tubulointerstitial disease of the kidneys that is associated with a high frequency of urothelial atypia, occasionally culminating in tumours of the renal pelvis and ur- ethra. Prevalence is very high in farmers living along the valley of the Danube and its tributaries. It has clear clinical and pathological simi- larities with Chinese herb nephropathy, and is likely to be caused in genetically predisposed people by exposure to aristolochic acid. 5-Aminosalicylic acid—used in the treatment of chronic inflam- matory bowel disease and causes clinical nephrotoxicity in approxi- mately 1 in 4000 patients/year. Inflammation can persist in the renal interstitium for months or years after stopping the drug, and renal impairment can continue to worsen even after the drug is stopped. Chronic interstitial nephritis in agricultural communities (CINAC)— nonproteinuric chronic kidney disease that presents in young, agri- cultural workers in Central America, Sri Lanka, India, Egypt, Tunisia, Senegal and Peru in the absence of any clear aetiology. The major risk factors are the combination of exposure to herbicides used in high quantities without any protection by agricultural workers in a hot climate. Presentation is with nonspecific symptoms. Urinalysis gen- erally shows low-level proteinuria but no haematuria. Histological features include tubular atrophy and fibrosis coupled with chronic glomerular changes. IgG4-related kidney disease—this refers to any form of renal involve- ment by IgG4-related disease, most commonly tubulointerstitial nephritis, which presents as acute or chronic renal insufficiency, renal mass lesions, or both, detectable by renal imaging. Lithium—the most common renal side effect is to cause nephrogenic diabetes insipidus. Long-term treatment does not af- fect the glomerular filtration rate in most patients, but 20% develop chronic renal insufficiency. It is likely that the serum concentration of lithium is important, and that renal damage is more probable if the serum concentration is consistently high, or if there are repeated episodes of lithium toxicity.

Radiation nephropathy—preventive shielding of the kidneys in patients receiving radiation therapy generally prevents radiation nephropathy, but total body irradiation preceding bone marrow transplantation leads 20% to develop chronic renal failure in the long term. Nephropathies induced by toxins. (1) Lead—a diagnosis of lead neph- ropathy should be considered in any patient with progressive renal failure, mild to moderate proteinuria, significant hypertension, a his- tory of gout, and an appropriate history of exposure. (2) Cadmium— exposure to high levels of cadmium is clearly toxic to the kidneys, but in the environmentally exposed population, its renal effects appear to be mild and not associated with progressive renal impairment. Nephropathies induced by metabolic disorders. (1) Chronic hypokalaemia—can induce interstitial fibrosis, tubular atrophy, and cyst formation that is most prominent in the renal medulla. (2) Chronic urate nephropathy—persistent hyperuricaemia can lead to the depos- ition of microtophi of amorphous urate crystals in the interstitium, with a surrounding giant cell reaction ('gouty nephropathy'). However, clinical evidence linking chronic renal failure to gout is weak; renal dysfunction can be documented only when the serum urate concen- tration is higher than 10 mg/dl (600 µmol/litre) in women and higher than 13 mg/dl (780 µmol/litre) in men for prolonged periods.

21.9.2 Chronic tubulointerstitial nephritis 4957 Drug-induced nephropathies Three well-described forms of drug-induced chronic interstitial nephritis—analgesic nephropathy, 5-aminosalicylic acid (5-ASA) nephropathy, and Chinese herb nephropathy—are compared and contrasted in Table 21.9.2.1, along with a fourth condition, Balkan endemic nephropathy (BEN). Analgesic nephropathy Analgesic nephropathy is a specific form of renal disease charac- terized by renal papillary necrosis and chronic interstitial nephritis caused by the prolonged and excessive consumption of analgesics. It is invariably caused by compound analgesic mixtures containing aspirin or other antipyretic agent in combination with phenacetin, paracetamol, or salicylamide, and caffeine or codeine in popular over-the-counter proprietary medicines. In the recent past, analgesic nephropathy was one of the com- moner causes of chronic renal failure, particularly in Australia and parts of Europe. Estimates made before phenacetin was removed from over-the-counter analgesics and before the enactment of le- gislation making combined analgesic preparations only available by prescription (in Sweden, Canada, and Australia) suggested that analgesic nephropathy was responsible for 13 to 20% of cases of endstage renal failure in Australia and some countries in Europe (such as Belgium and Switzerland). In the United States of America as a whole, a prevalence of 1 to 3% was found, and in areas of North Carolina, up to 10%. During the 1990s, there was a clear decrease in the prevalence and incidence of the condition among patients under- going dialysis in several European countries and Australia. Most au- thors have associated this decrease with the removal of phenacetin from analgesic mixtures, but it is impossible to draw definitive con- clusions from the epidemiological observations since other factors, such as eligibility criteria for dialysis treatment and the availability of remaining analgesic mixtures, may also have had an influence. The presence of analgesic nephropathy further decreased in recent years with incidence rates in patients starting chronic renal replacement therapy of 2.2% in Belgium (2008), 1.6% in Australia (2010), and 0.2% in the United States (2011). In developing countries, however, first data in dialysis patients were recently reported with prevalences of 3.5% in Sudan, 5% in Saudi Arabia, and 5% in Egypt. Pathogenesis and pathology The aetiology of analgesic nephropathy remains controversial, and the question of which kinds of analgesic are nephrotoxic is still a matter of debate. Experimental studies, mainly using rats fed with large amounts of drugs, sometimes aggravating the renal effects by dehydration or by introducing sepsis, have produced results that have been difficult to interpret, but it could be concluded that renal papillary necrosis was most frequently observed

after the adminis- tration of aspirin in combination with phenacetin or paracetamol. In humans, the long-standing excessive use of analgesics observed in patients with analgesic nephropathy is preferentially that of anal- gesic mixtures rather than single agents, with abusers taking these products for their mood-altering effects rather than for the relief of physical complaints, hence all these mixtures contain caffeine and/ or codeine, substances that can create psychological dependence. In most of the early reports of analgesic nephropathy, nearly all pa- tients had taken large amounts of analgesic mixtures containing phenacetin. In a variety of case–control studies, patients with renal failure ranging from newly diagnosed chronic kidney disease (CKD, stages 1–3) to endstage renal disease, and the specific diagnosis of renal papillary necrosis, have been compared with a variety of controls. The definition of ‘minimal analgesic abuse’ has varied consider- ably, from a frequency of twice a week to daily, and from a period of 1 month to 1 year. However, overall the findings show that analgesic abuse is associated with an exceptionally high relative risk of 17.2 with regard to papillary necrosis, a risk of between 2.2 and 2.9 with regard to CKD or endstage renal failure in four studies, and with nonconclusive results in other studies. The mechanisms responsible for renal injury are incompletely understood. The final injury is most probably due to both the Table 21.9.2.1 Differential diagnosis of some forms of chronic interstitial nephritis Analgesic nephropathy 5-Aminosalicylic acid nephritis Chinese herb nephropathy Balkan endemic nephropathy Course

> 10–15 years 6 months 6 months–2 years 20 years Kidney imaging Shrunken, irregular contours, papillary calcifications Slightly shrunken, smooth, no calcifications Shrunken, irregular con- tours, no calcifications Shrunken, smooth surface, no calcifications Histology: • Cellular infiltration ++ +++

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• Fibrosis ++ ++ ++ ++ • Atrophy ++ + ++ +++ Capillary sclerosis + ?– ?/+ + Apoptosis ? ? ? + Urothelial malignancies +a – + + Familial occurrence – – – + Aetiology Analgesics + addictive substances 5-ASA + additional factors Aristolochic acid + vaso- active substances Aristolochic acid + genetic predisposition a As long as phenacetin was part of the analgesic mixture.

section 21 Disorders of the kidney and urinary tract 4958 haemodynamic and cytotoxic effects of phenacetin metabolized to acetaminophen and aspirin converted to salicylate, resulting in pap- illary necrosis and interstitial fibrosis (Fig. 21.9.2.1). The renal damage induced by analgesics is most prominent in the medulla. The earliest changes consist of thickening of the vasa recta capillaries (capillary sclerosis) and patchy areas of tubular necrosis; similar vascular lesions can be found in the renal pelvis and ureter, suggesting that the primary effect is damage to the vascular endothe- lial cells. Later changes include areas of papillary necrosis and sec- ondary cortical injury, with focal and segmental glomerulosclerosis and interstitial infiltration and fibrosis.
Clinical features The renal manifestations of analgesic nephropathy are usually nonspecific; renal function is normal or there is slowly progressive chronic renal failure, and urinalysis may be normal or may reveal sterile pyuria and mild proteinuria (<1.5 g/day). Hypertension and anaemia are commonly seen with moderate to advanced disease. Most patients have no symptoms referable to the urinary tract, al- though flank pain or macroscopic/microscopic haematuria from a sloughed or obstructing papilla may occur. Urinary tract infection is also somewhat more common in women

with this disorder. Despite the nonspecific nature of the renal presentation, there are frequently other findings that point towards the presence of analgesic nephropathy. Most patients are female and between the ages of 30 and 70 years. Careful questioning often reveals a history of chronic headaches or low back pain that leads to the analgesic use. Also common are other somatic complaints (such as malaise and weakness), and ulcer-like symptoms or a history of peptic ulcer disease due in part to chronic aspirin ingestion. The decline in renal function can be expected to progress if an- algesics are continued, whereas renal function stabilizes or slightly improves in most patients if analgesic consumption is discontinued. However, if the renal disease is already advanced, then progres- sion may occur in the absence of drug intake, presumably due to secondary haemodynamic and metabolic changes associated with nephron loss. The late course of analgesic nephropathy may also be complicated by urinary tract malignancy, which will develop in as many as 8 to 10% of patients with analgesic nephropathy. The tumours generally become apparent after 15 to 25 years of analgesic abuse, usually but not always in patients with clinically evident analgesic nephropathy. Most patients are still taking the drug at the time of diagnosis, but clinically evident disease can first become apparent several years after cessation of analgesic intake and even after renal transplant- ation. The main presenting symptom of urinary tract malignancy in patients with analgesic nephropathy is microscopic or gross haema- turia, hence continued monitoring is essential, and new haematuria should be evaluated by urinary cytology and, if indicated, cystoscopy with retrograde pyelography. The incidence of urothelial carcinoma after renal transplantation in patients with analgesic nephropathy is comparable to the incidence (up to 10%) of urothelial carcinomas in patients with endstage renal failure due to analgesic nephrop- athy. Removal of the native kidneys before renal transplantation has been suggested, but the efficacy of this regimen has not been proven. Moreover and regardless of an established diagnosis of analgesic nephropathy, analgesic abuse as such forms an increased risk for the development of cancers of the kidney and urinary tract in patients on dialysis and after transplantation. Diagnosis and treatment The lack of reliable criteria for diagnosis and yet the apparent high prevalence of analgesic nephropathy during the 1980s in Belgium (17.9% in 1984) led us to perform a series of prospective multicentre controlled studies to define and validate the diagnostic criteria for this disease. We provided strong evidence that specific anatomical changes, best seen by noncontrast CT scan, have much greater sen- sitivity and specificity than other clinical signs and symptoms in the diagnosis of endstage renal disease due to analgesic nephrop- athy. These changes are (1) a decrease in renal volume, (2) bumpy renal contours, and (3) papillary calcifications (Fig. 21.9.2.2). These observations were validated in a representative sample of patients with analgesic abuse with endstage renal disease and extended to patients with moderate renal failure. Papillary calcifications had the highest sensitivity and specificity.
A decrease in volume com- bined with bumpy contours and/or papillary calcifications showed a sensitivity of 90% and a specificity of 90% in patients with endstage renal failure, and a sensitivity of 77% and a specificity of 100% in those with moderate renal failure. In clinical practice, however, it is important to remember that the predictive value of this test, like any other diagnostic test, is very much dependent on the prevalence of the disease in the population under study. It should therefore be Synergistic toxicity of analgesics in the renal inner medulla Aspirin MFO Cyt p450 Paracetamol Renal papillary concentration Prostaglandin synthase Salicylate Glutathione depletion N-acetyl-p-benzoquinoneimin Arylation of renal papillary protein

- oxidative stress Renal papillary necrosis Paracetamol undergoes oxidative metabolism by prostaglandin H synthase to reactive quinoneimine that is conjugated to glutathione. If

paracetamol is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the paracetamol is ingested with aspirin, the aspirin is converted to salicylate and salicylate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. With the cellular glutathione depleted, the reactive metabolite of paracetamol then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae. Centrally acting dependence producing drugs Caffeine ± 50 mg Codeine 10–30 mg Analgesic nephropathy Renal papillary concentration Phenacetin Fig. 21.9.2.1 Synergistic toxicity of analgesics in the renal inner medulla and centrally acting dependence-producing drugs leading to analgesic nephropathy. Reproduced with permission from Kincaid-Smith P, Nanra RS (1993). In: Schrier RW,
Gottschalk CW, eds. Diseases of the kidney, pp 1099–129. Little, Brown and Company, Boston, MA, and Duggin G (1996). American Journal of Kidney Diseases 28/1 (Suppl. 1), S39–S47.

 utilized in patients with a reasonable risk for analgesic nephropathy and not as a general screening test. As indicated previously, patients with normal or only mildly/ moderately impaired renal function should be strongly encouraged to stop taking analgesics in the hope that further deterioration in renal function can be avoided. Those with severe or endstage renal failure will not recover renal function, although there may be other valid medical reasons for recommending that they stop ingesting large quantities of analgesics. The medical management of chronic renal failure is along conventional lines, as is provision of renal replacement therapy. Nonsteroidal anti-inflammatory drugs Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular for treating a wide range of clinical conditions and are available both over the counter and on prescription. Despite their usefulness, there is substantial evidence from experimental and clinical studies that they have a variety of effects on the kidney. The most common renal disorder associated with NSAIDs is acute, largely reversible, insuffi- ciency due to the inhibition of renal vasodilatory prostaglandins in the clinical setting of a stimulated renin–angiotensin system. Older age, hypertension, concomitant use of diuretics or aspirin, pre-existing renal failure, diabetes, and plasma-volume contraction are known risk factors for renal failure after the ingestion of NSAIDs. Less commonly, NSAIDs may cause acute interstitial nephritis with proteinuria. NSAIDs may worsen the underlying hyperten- sion. Electrolyte and fluid abnormalities including hyperkalaemia, hyponatraemia, and oedema may occur. In contrast to the well-characterized acute effects of NSAIDs on the kidney, the chronic effects are less well documented. However, NSAIDs are the most frequent cause of permanent renal insufficiency after acute interstitial nephritis. Risk factors for irreversible failure are pre-existing renal damage, long-standing intake of the causative drug, slow oligosymptomatic disease development, and histological signs of chronicity with those of acute interstitial nephritis. Although renal papillary necrosis and chronic renal failure can occur after the prolonged use of NSAIDs, the actual risk of these serious compli- cations is unknown. The frequency of renal papillary necrosis in the context of NSAID intake as a primary or contributing cause of endstage renal disease is also unknown, but most likely very low. Aristolochic acid nephropathies Until recently, two types of chronic interstitial nephritis were con- sidered as two separate entities named respectively Chinese herb nephropathy and BEN. The cause of Chinese herb nephropathy was from the time of its clinical detection attributed to the consumption of a plant, Aristolochia fangchi, which contained the nephrotoxin aristolochic acid. By contrast, the aetiology of BEN was for decades the subject of many

hypotheses. However, clinical, histopathological, epidemiological, and toxicological data convincingly suggest that long-term exposure to aristolochic acid-contaminated food is the aetiological factor in BEN, such that aristolochic acid nephropathy has been proposed as a more correct term for this condition. Aristolochic acid nephropathy—Chinese herb nephropathy In 1992, physicians in Belgium noted an increasing number of women presenting with renal failure, often near endstage, following their exposure to a slimming regimen containing Chinese herbs. An initial survey of seven nephrology centres in Brussels identi- fied 14 women under the age of 50 who had presented over a 3-year period with advanced renal failure due to biopsy-proven chronic tubulointerstitial nephritis, nine of whom had been exposed to the same slimming regimen. As of early 2000, a total of more than (a) Diagnostic criteria used (b) CT scans RA Right kidney B Decreased: A + B <103 mm (males) <96 mm (females) Bumpy contours 0 1–2 3–5

> 5 B A SP A RA Left kidney Moderate renal failure Endstage renal failure RV Renal size Indentations Papillary calcifications Fig. 21.9.2.2 Diagnostic criteria of analgesic nephropathy.

section 21 Disorders of the kidney and urinary tract 4960 (b) (a) Fig. 21.9.2.3 Renal biopsy from a patient with Chinese herb nephropathy showing tubular atrophy, widening of the interstitium, cellular infiltration, and fibrosis, with glomeruli surrounded by a fibrotic ring. Masson staining (a), haematoxylin and eosin staining (b). 120 cases had been identified. The epidemiology is unknown, as is the risk for the development of severe renal damage, but the recent publication of case reports from several countries in Europe and Asia would seem to indicate that the incidence of herbal medicine- induced nephrotoxicity is more common than previously thought. Pathogenesis and pathology The aetiology of Chinese herb nephropathy is aristolochic acid found in the Aristolochia plant. However, in addition to aristolochic acid, patients with ‘Chinese herb nephropathy’ detected in the Brussels area also received the appetite suppressants fenfluramine and diethylpropion, which have vasoconstrictive properties, and acetazolamide, which alkalinizes the urine, thereby potentially enhancing the nephrotoxic effect of aristolochic acid, although a re- cent experimental study did not support this hypothesis. Another uncertain factor is why only some patients exposed to the same herbal preparations develop renal disease. Women ap- pear to be at greater risk than men, and other factors that might be important include toxin dose, batch-to-batch variability in toxin content, individual differences in toxin metabolism, and a genet- ically determined predisposition towards nephrotoxicity and/or carcinogenesis. The main histological lesion, which is located principally in the cortex, is extensive interstitial fibrosis with atrophy and loss of the tubules (Fig. 21.9.2.3). Cellular infiltration of the interstitium is scarce. Thickening of the walls of the interlobular and afferent ar- terioles results from endothelial cell swelling. The glomeruli are rela- tively spared and immune deposits are not observed. These findings suggest that the primary lesions may be centred in the vessel walls, thereby leading to ischaemia and interstitial fibrosis. At one centre in Belgium, 19 native kidneys and ureters were removed in a series of 10 patients during and/or after renal trans- plantation. Multifocal, high-grade, flat, transitional cell carcinoma (carcinoma in situ) was observed in four (40%), while all had multi- focal moderate atypia. Tissue samples revealed aristolochic acid- related DNA adducts, indicating a possible mechanism underlying the development of malignancy. In another study of 39 patients with Chinese herb nephropathy and endstage renal disease who underwent prophylactic removal

of the native kidneys and ureters, urothelial carcinoma was discovered in 18 and mild to moderate urothelial dysplasia in 19. All atypical cells were found to overexpress a p53 protein, suggesting the presence of a mutation in the gene. Clinical features Patients present with renal insufficiency and other features indicating a tubulointerstitial disease. Blood pressure is either normal or only mildly elevated, and the urinary sediment reveals only a few red and white cells. The urine contains protein (<1.5 g/ day), consisting of both albumin and low molecular weight pro- teins that are normally reabsorbed by the proximal tubules, hence tubular dysfunction—also marked by glycosuria—contributes to the proteinuria. The plasma creatinine concentration at presen- tation has ranged from 1.4 to 12.7 mg/dl (123–1122 µmol/litre). Follow-up studies have revealed relatively stable renal function in most patients with an initial plasma creatinine concentra- tion below 2 mg/dl (176 µmol/litre) once the intake of the drug has been stopped. However, progressive renal failure resulting in eventual dialysis or transplantation may ensue in patients with more severe disease, even if further exposure to Chinese herbs is prevented. A similar clinical and pathological process has been reported in a group of patients from Taiwan who had ingested a selec- tion of uncontrolled traditional Chinese herbs that differed from those of the slimming regimen. Despite discontinuation of these remedies, progressive renal failure was common. In recent years, this disease has been diagnosed in many countries throughout the world, particularly in mainland China. Diagnosis and treatment There are no specific criteria for the diagnosis of this type of renal disease. The condition should be suspected in any patient with un- explained relatively rapidly progressive renal disease who is using/ abusing herbal remedies. The presence of tubular proteinuria may be a clue to the diagnosis, particularly in the early stages. The histo- logical appearances are not specific, but renal biopsy is necessary to exclude other conditions in this clinical context.

21.9.2 Chronic tubulointerstitial nephritis 4961 There is no proven effective therapy for this disorder, which typ- ically presents with marked interstitial fibrosis without prominent inflammation, although an uncontrolled study suggested that cor- ticosteroids may slow the rate of loss of renal function. The high incidence of cellular atypia of the genitourinary tract suggests that, as a minimum, these patients should undergo regular surveillance for abnormal urinary cytology. Whether more aggressive manage- ment strategies, such as bilateral native nephroureterectomies (par- ticularly in those undergoing renal transplantation), are required is unclear. Findings from a recent report support the more aggressive option. Renal transplantation is an effective modality for those who progress to endstage renal disease; one report noted no recurrence in five patients. Aristolochic acid nephropathy—Balkan endemic nephropathy BEN is a chronic, familial, noninflammatory tubulointerstitial disease of the kidneys that is associated with a high frequency of urothelial atypia, occasionally culminating in tumours of the renal pelvis and urethra. Epidemiology As the name suggests, BEN is most commonly seen in south-eastern Europe, including the areas traditionally considered to comprise the Balkans, that is, Serbia, Bosnia and Herzegovina, Croatia, Romania, and Bulgaria. It is most likely to occur among those living in the valley of the Danube river and its tributaries, a region in which the plains and low hills generally have a high humidity and rainfall (Fig. 21.9.2.4). There is a very high prevalence in endemic areas, with rates ranging between approximately 0.5 and 4.4%, increasing to as high as 20% if the disorder is suspected and carefully screened for among an at-risk population. The prevalence of BEN has remained stable over the last 40 to 50 years in two of the sites where the con- dition was first recognized. A striking observation is that nearly all affected patients are farmers. Pathogenesis Environmental factors Given that the condition is endemic to a specific geographic area, toxins

and/or environmental exposures that are unique to the Balkans have been investigated for many years. In 1969, Ivić proposed that ingestion of flour contaminated with seeds from Aristolochia clema- titis may be the cause of BEN. He noted that seeds from these plants, which grew abundantly in local wheat fields, comingled with wheat grain during the harvesting process. He administered Aristolochia seeds to animals, which developed renal damage, and speculated that human exposure to a toxic component of Aristolochia seeds could occur through ingestion of bread prepared with flour derived from contaminated grain. However, his field surveys and data failed to provide convincing evidence, and his astute observations were neglected for many decades. The clinical expression and pathological lesions observed at dif- ferent stages of Chinese herb nephropathy and BEN are strikingly similar, except for their rate of progression towards endstage renal failure, but recognition that aristolochic acid was implicated in the pathogenesis of BEN followed the finding by Grollman and col- leagues of aristolochic acid-derived DNA adducts in renal cortical and urothelial tumour tissue of patients, with dominance of A:T and T:A transversions in the TP53 tumour suppressor gene mutational spectrum. The evidence has been further strengthened by the obser- vation that mutational spectra in urothelial cancers among BEN pa- tients resemble the mutational ‘signature’ observed in cultured cells and rodents treated with aristolochic acid. Genetic factors Support for a genetic component to aetiology includes observa- tions that the disease clearly affects particular families, and that some ethnic populations who have lived in endemic areas for gen- erations do not develop BEN. The mode of inheritance has not yet been established and possible causative gene(s) have not been identified, but a locus in the region between 3q25 and 3q26 has SLOVENIA HUNGARY CROATIA BOSNIA SERBIA ROMANIA BULGARIA ALBANIA MONTENEGRO Sava Zagreb Danube Sarajevo Sofia Sava M o rav a D a n u b e Belgrade Fig. 21.9.2.4 Foci of Balkan endemic nephropathy.

 been incriminated. However, some observations are inconsistent with a genetic basis. First, BEN is observed in individuals who have immigrated into the Balkan area from regions without the disorder, and in previously unaffected families who have lived for at least 15 years in endemic areas. Second, BEN does not develop in members from previously affected families who have left en- demic areas early in life or who spent less than 15 years in these areas. An obvious unifying hypothesis is that the disease occurs in genetically predisposed individuals who are chronically exposed to aristolochic acid. Pathology In the early stages of disease, renal histology reveals focal cortical tubular atrophy, interstitial oedema, and peritubuloglomerular sclerosis with limited mononuclear cell infiltration. Narrowing and endothelial swelling of interstitial capillaries (e.g. capillary sclerosis) is also described. In advanced cases, marked tubular at- rophy and interstitial fibrosis develop along with focal segmental glomerular changes and global sclerosis. There is an extremely high incidence of cellular atypia and urothelial carcinoma of the genitourinary tract. Clinical features BEN is a slowly progressive tubulointerstitial disease that may cul- minate in endstage renal disease. Clinical manifestations first appear between 30 and 50 years of age, with findings before the age of 20 being extremely rare. One of the first signs is tubular dysfunction, which is characterized by an increased excretion of low molecular weight proteins (such as β2-microglobulin). Early tubular injury can also lead to renal glycosuria, aminoaciduria, and diminished ability to handle an acid load. Over a period of more than 20 years there is a progressive decrease in concentrating ability (resulting in polyuria) and in the glomerular filtration rate (resulting in endstage renal disease). Patients are usually without oedema and normo- tensive, with hypertension only developing with endstage disease. A normochromic normocytic anaemia occurs with early disease, which becomes

increasingly pronounced as the disorder progresses. Urinary tract infection is rarely observed. Kidneys are of normal size early in the course of the disease, but a symmetrical reduction of kidney size with a smooth outline and normal pelvicalyceal system is subsequently observed in patients with late-stage disease. Intrarenal calcifications are not seen. BEN is also associated with the development of transitional cell carcinoma of the renal pelvis or ureter, with studies noting a wide range in incidence (from 2 to nearly 50%). These tumours are gener- ally superficial and slow-growing. Diagnosis and treatment The diagnosis of BEN is based on the presence of some combination of the following findings: • Symmetrically shrunken kidneys with absence of intrarenal calcifications • Farmers living in the villages where BEN occurs • Familial history positive for BEN • Mild tubular proteinuria and hyposthenuria (inability to concen- trate the urine normally) • Normochromic/hypochromic anaemia occurring in patients with only slightly impaired renal function Since it has been demonstrated that Chinese herb nephropathy and Balkan endemic nephropathy have a common aetiological factor, i.e. aristolochic acid containing food (bread) or pills (slim- ming regimens), primary prevention can be considered. The high incidence of cellular atypia in the genitourinary tract suggests that regular surveillance should be performed for abnormal urinary cytologies. Whether bilateral native nephroureterectomies are required, particularly in those undergoing renal transplantation, is unclear. 5-Aminosalicylic acid There is an association between the use of 5-ASA in patients with chronic inflammatory bowel disease and the development of a par- ticular type of chronic tubulointerstitial nephritis. For many years, sulfasalazine, an azo-compound derived from sulfapyridine and 5-ASA, the latter being the pharmacologically active moiety, was the only valuable noncorticosteroid drug in the treatment of inflammatory bowel disease. Since the therapeutic- ally inactive sulfapyridine moiety was largely responsible for the mainly haematological side effects of sulfasalazine, this stimulated the development of several new 5-ASA formulations (mesalazine, olsalazine, balsalazide) for topical and oral use. These new 5-ASA products replaced sulfasalazine as the first-line therapy for mildly to moderately active inflammatory bowel disease. However, a literature search revealed 17 published cases of renal impairment associated with 5-ASA therapy in patients with inflammatory bowel disease, and in several it was shown that this did not recover completely on stopping the drug, even after a follow-up period of several years. In a retrospective study, nephrologists reported 40 patients with inflam- matory bowel disease showing renal impairment, including 15 cases with interstitial nephritis and previous use of 5-ASA. Stimulated by these findings we started a European prospective registration study aiming to register all patients with inflammatory bowel disease and renal impairment and to control for a possible association with 5- ASA therapy. A cohort of 1449 patients with inflammatory bowel disease seen during 1 year in the outpatient clinics of 28 European gastroenterology departments was investigated. Preliminary re- sults showed 30 patients (2%) with decreased renal function, and a possible association with 5-ASA therapy was found in one-half of them. A recent study estimated the incidence of clinical nephrotox- icity in patients taking 5-ASA as 1 in 4000 patients/year. However, determining the cause of renal disease in those with in- flammatory bowel disease is not straightforward. The most frequent renal complications are oxalate stones and their consequences, such as pyelonephritis, hydronephrosis, and (in the long term) amyloid- osis. Chronic inflammatory bowel disease is also associated with glomerulonephritis and minimal-change glomerulonephritis, mem- branous, membranoproliferative, and focal glomerulosclerosis, and proliferative crescentic glomerulonephritis have all been reported. As for many drugs, reversible acute interstitial nephritis has been described with the use of 5-ASA compounds. In view of this com- plexity, the association of 5-ASA and chronic interstitial nephritis in patients with inflammatory bowel disease can be

difficult to in- terpret, since renal involvement may be an extraintestinal mani- festation of the underlying disease. However, the particular form of chronic tubulointerstitial nephritis in patients with inflammatory bowel disease treated with 5-ASA is characterized by an important cellular infiltration of the interstitium with macrophages, T cells, and also B cells (Fig. 21.9.2.5).

21.9.2 Chronic tubulointerstitial nephritis 4963 Pathogenesis and pathology That 5-ASA causes renal disease is supported by the number of case reports in the literature of patients with inflammatory bowel disease using 5-ASA as their only medication, the improvement (at least partially) of impaired renal function on stopping the drug, and a worsening after resuming 5-ASA use. Furthermore, the molecular structure of 5-ASA is very close to that of salicylic acid, phenacetin, and aminophenol, drugs with well-documented nephrotoxic po- tential (Fig. 21.9.2.1). Calder and colleagues found that necrosis of the proximal convoluted tubules and papillary necrosis developed in rats after a single intravenous injection of 5-ASA at doses of 1.4, 2.8, and 5.7 mmol/kg body weight (high pharmacological doses). The mechanism of renal damage, possibly caused by 5-ASA itself, may be analogous to that of salicylates by inducing hypoxia of renal tissues, either by uncoupling oxidative phosphorylation in renal mitochondria by inhibiting the synthesis of renal prostaglandins, or by rendering the kidney susceptible to oxidative damage by a redu- cing renal glutathione concentration after inhibition of the pentose phosphate shunt. Clinical features A typical case is shown in Fig. 21.9.2.5. An intriguing aspect of this type of toxic nephropathy is the documented persistence of the renal interstitium inflammation even several months/years after first taking the drug. The disease is more prevalent in men, with a male- to-female ratio of 15:2. The age of patients in reported cases ranges from 14 to 45 years. By contrast with analgesic nephropathy, where renal lesions are only observed after several years of analgesic abuse, interstitial nephritis associated with 5-ASA was observed during the first year of treatment in 7 out of 17 reported cases; most of these patients had started 5-ASA therapy with documented normal renal function. In several patients, particularly those in whom there was a delayed diagnosis of renal damage, recovery of renal function did not occur, and some needed renal replacement therapy. Diagnosis and treatment Since this type of chronic tubulointerstitial nephritis produces few if any symptoms, and if diagnosed at a late stage progresses to irrevers- ible chronic endstage renal disease, serum creatinine levels should be measured in any patient with inflammatory bowel disease treated with 5-ASA at the start of the treatment, every 3 months for the re- mainder of the first year, and annually thereafter. The use of con- current immunosuppressive therapy, as is the case in severe forms of chronic inflammatory bowel disease, may necessitate extension to the period of intensive renal function monitoring. If serum cre- atinine increases, a renal biopsy is the only way to demonstrate the cause. Chronic interstitial nephritis in agricultural communities The main causes of CKD in developed countries are diabetes and hypertension, associated with ageing and obesity; this is also true in some developing countries. In addition to these ‘traditional’ causes, glomerular and tubulointerstitial diseases due to infections, C.P. man born 19.01.1971 0 2 4 6 8 10 12 1.1 10.6 4.9 4.2 Serum Creatinine (mg/dl) 32 mg/day HAEMODIALYSIS Methylprednisolone 16 mg/day Pentasa® 3x500 mg/day orally 4.0 3.9 3.8 03/10/91 15/03/92 23/02/94 02/03/94 22/11/94 02/12/94 06/01/95 01/05/96 01/12/96 08/05/99 22/12/94 31/12/94 05/08/00 16/08/01 4.3 5.3 Potassium (mEq/L): 03/08/02 5.4 15/03/05 7.3 HAEMODIALYSIS (a) (c) (c) (b) (b) 3.3 3.3 renal biopsy renal biopsy IBD diagnosis 2.6 2.8
Fig. 21.9.2.5 Nephrotoxicity in a patient treated with 5-aminosalicylic acid for inflammatory bowel disease (IBD). (a) Evolution of renal failure. (b) First renal biopsy showing widening and massive cellular infiltration of the interstitium, tubular atrophy, and relative spacing of glomeruli. The

cellular infiltration was identified using appropriate monoclonal antibodies and consisted not only of T cells and macrophages but also of B cells. (c) A second renal biopsy performed after the drug had been stopped for 8 months, when there was a modest improvement in renal function, again showed a significant cellular infiltration of the interstitium, tubular atrophy, and fibrosis. Thirteen years after the diagnosis of chronic interstitial nephritis was made in this young man, who had documented normal renal function at the start of treatment, haemodialysis had to be started. He is now on the waiting list for renal transplantation.

section 21 Disorders of the kidney and urinary tract 4964 nephrotoxic drugs, herbal medications, environmental toxins, and occupational exposure to pesticides—the so-called nontraditional causes—contribute to the CKD burden in developing countries. However, since the 1990s, an increase in CKD prevalence not as- sociated with traditional risk factors has been reported, primarily affecting agricultural communities and male agricultural workers. This new disease, chronic interstitial nephritis in agricultural com- munities (CINAC), has become an important health problem in many countries, including El Salvador, Nicaragua, Guatemala, Costa Rica, Sri Lanka, Egypt, India, Tunisia, Senegal, and Peru. Epidemiology In Central America, growing numbers of CKD patients and in- creased CKD mortality have been observed over the last two dec- ades, particularly in Nicaragua and El Salvador. The Pan American Health Organization has reported CKD-specific mortality (deaths per 100 000 population associated with CKD stages 3a, 3b, 4, and 5) in the region: Nicaragua (42.8), El Salvador (41.9), Guatemala (13.6), and Panama (12.3). These figures are four times the global CKD mortality rate, and up to 17 times greater than the lowest CKD mortality reported in the Americas region. As for gender, mortality rates in men are three times those of women. CKD in Central America affects mainly young men, between the third and fifth decades of life, working in agriculture (mainly sugarcane or other agricultural activities at lower altitudes and con- sequent higher temperatures). Women are less affected than men, but CKD prevalence in women is higher than CKD prevalence seen in international studies. Recent information demonstrated that CKD related mortality, rates in women and children in Ecuador and Nicaragua were up to 9 times higher was compared to control coun- tries in the area. This suggests that the heat stress hypothesis cannot fully explain this CINAC epidemy. In El Salvador farming communities the prevalence of CKD among adults is 15 to 21%. Of the patients studied, less than half have diabetes or hypertension; males predominate, and renal damage begins early in life. Women, men, adolescents, and children who live in farming communities are affected, whether they work in the fields or not; and people living in highlands and lowlands are all at risk. Environmental and occupational investigations demonstrate the presence of pesticides and heavy metals (cadmium and arsenic) in well water, dirt floors in homes, and farmlands (being more con-centrated in fields under cultivation). In addition, farmers carrying out intense physical activity during long hours exposed to high tem- peratures, with insufficient hydration and unprotected use of agro- chemical agents are more vulnerable to develop CINAC. Various terms are used for CINAC in the medical literature: CKD of unknown origin, CKD of uncertain origin, CKD of unknown aeti-ology, or agrochemical nephropathy. In some cases, it is named for the region or country where it appears: Central American nephrop- athy, Salvadoran agricultural nephropathy, Mesoamerican endemic nephropathy, chronic tubulointerstitial kidney disease of Central America, Udhanam endemic nephropathy (India), or Sri Lankan agricultural nephropathy. Diagnosis There is no consensus on a case definition for CINAC, The diag- nosis is presumed when patients fulfill CKD criteria in the absence of diabetes, hypertension, glomerular proteinuric disease, poly- cystic kidneys, obstructive uropathy, or other recognized causes, in conjunction with three general

conditions—poverty with all its repercussions, unhealthy working conditions, and a contaminated environment. In Sri Lanka, CINAC is defined as CKD in the absence of a past history of diabetes, chronic or severe arterial hypertension, snake bite, or glomerulonephritis or other urinary tract disease, and with normal glycosylated haemoglobin (<6.5%) and blood pressure less than 160/100 mmHg in untreated patients or less than 140/ 90 mmHg in patients receiving up to two antihypertensive drugs. Clinical features The disease emerges in the context of social determinants led by poverty and its consequences, and provokes a profound psycho- logical impact on patients and the community. CINAC is usu- ally asymptomatic and presents with slowly progressive renal impairment. Some of the general symptoms reported in early stages of the disease include arthralgia, asthenia, decreased libido, cramps, and fainting. Regarding renal symptoms, disorders of micturition are most common: nocturia, dysuria, post-void dribbling, urinary hesi- tancy, and foamy urine. All symptoms appear as early as CKD stage 2 and tend to increase as the disease advances. Blood pressure is either normal or only mildly elevated. Tendon reflex abnormalities are seen as early as CKD stage 2. Sensorineural hearing loss may be evident. Fundoscopic examination, intraocular pressure, and visual fields tests are mostly normal. As for markers of renal damage, the urine sediment shows no significant abnormalities or dysmorphic erythrocytes. Proteinuria, mostly moderate, can be observed. Excretion of tubular proteins such as β2-microglobulin and neutrophil gelatinase-associated lipocalin (NGAL) are elevated, suggesting tubular dysfunction. Analysis of a 24-h urinary collection typically shows polyuria char- acterized by hypermagnesuria, hyperphosphaturia, hypernatriuria, hyperkaliuria, and hypercalciuria. Fractional excretion of magne- sium and sodium is increased. Serum electrolytes reflect the excess excretion observed in urine. Blood osmolality is normal, as (usually) is the urinary osmolality. The predominant acid–base balance dis- order reported is a metabolic alkalosis. Acid–base and electrolyte disorders in urine and blood begin to appear in CKD stage 2. The absence of acidosis could indicate a relative conservation of the distal segment of the nephron, with bicarbonate reabsorption and hydrogen ion excretion. Renal ultrasound imaging shows increased echogenicity, a decreased corticomedullary ratio, and irregular renal margins. Renal Doppler ultrasonography reports normal blood flow in renal arteries, segmental arteries, and renal parenchyma. Doppler ultrasound examination of peripheral arteries is more likely to reveal changes of atherosclerosis in the tibial artery than the ca- rotid and aortoiliac arteries. One hypothesis for this selective damage to tibial arteries could be their greater occupational con- tact with toxic substances. Farmers’ legs, sometimes bare, are the parts most exposed to agrochemicals from spraying, which is done using backpack applicators at high ambient temperatures, with consequent vasodilation and opening of skin pores. Paddy farmers immerse their legs long periods in agrochemical rich muddy soil.

21.9.2 Chronic tubulointerstitial nephritis 4965 Pathogenesis and pathology The morphological pattern described is a chronic tubulointerstitial nephropathy with secondary glomerular and vascular damage. The main findings are interstitial fibrosis and tubular atrophy, with or without inflammatory monocyte infiltration. In addition, generalized sclerosis, increased glomerular size, collapse of some glomerular tufts, and lesions of extraglomerular blood vessels (such as intimal proliferation and thickening and vacuolization of the tunica media) are also observed. This pattern is consistent with tubulointerstitial nephritis, but in different degrees depending on sex (greater in males than females), occupation (greater in sugarcane agricultural workers than nonsugarcane agricultural workers, and lesser in nonagricultural workers) and CKD stage. There are nonspecific deposits of IgM, C3, and C1q in the glomeruli, but no immunoglobulin deposits in the tubules or interstitium. In add- ition to the known histopathology, a unique constellation of lesions was

identified. At EM, proximal tubular cells (PTCs) demonstrated large dysmorphic lysosomes with a light-medium electron dense ma- trix containing dispersed dark electron-dense non-membrane bound ‘aggregates’, and were histologically associated with varying degrees of cellular/tubular atrophy, apparent cell fragments shedding and no to weak PTC proliferative capacity (Fig. 21.9.2.6). Aetiology Two aetiological hypotheses for CINAC in Central America—both multifactorial but emphasizing different primary triggers—have been proposed: one related to heat stress with repeated episodes of rhabdomyolysis and dehydration; the other related to toxic exposures (pesticides) at work and in the environment of agricultural commu- nities. In Sri Lanka, a similar hypothesis has been developed, in which multiple heavy metals act synergistically with agrochemicals such as glyphosate and their residues. A recent meta-analysis indicated that there is no consistent evidence to support an association between, CKD and heat stress/dehydration. In contrast, a consistent evidence for the adverse effect of agrochemicals and CKD was observed. The presence of extrarenal clinical manifestations (neurological, hearing, and lower limb arteries) supports arguments for a toxic causal factor (heavy metals, chemical or microbial substances), with (a) (b) (c) (d) 20 µm 3 µm 1 µm 30 µm * * * * * * Fig. 21.9.2.6 (a) Proximal tubule (asterisk) demonstrating accumulation of enlarged intracellular argyrophylic granules (Jones silver stain). (b) Fluorescent staining for the lysosomal marker Cathepsin B demonstrating increased fluorescence in some tubules (asterisks). Insert: Jones silver staining of the white marked region demonstrating that Cathepsin B positive granules are argyrophylic. (c) Electron microscopic image of proximal tubular cells containing enlarged dysmorphic granules, consistent with lysosomes, and containing dispersed electrondense aggregates. (d) detail of white marked region in c. Images from Sri Lankan CINAC patients.

section 21 Disorders of the kidney and urinary tract 4966 Table 21.9.2.2 Major organ manifestations of IgG4-related disease Pancreas Type 1 autoimmune pancreatitis Salivary glands Sialadenitis Eye/orbit/lachrymal glands Orbital inflammation/pseudotumour and dacryoadenitis Aorta/artery/ retroperitoneum Periaortitis/periarteritis and retroperitoneal fibrosis Kidney Tubulointerstitial nephritis and pyelitis Lymph nodes Lymphadenopathy Lung Lung disease (inflammatory pseudotumour, alveolar interstitial disease, and pleuritis) Biliary system Sclerosing cholangitis and cholecystitis Liver Pseudotumour and hepatopathy Central/peripheral nervous system Pachymeningitis and infraorbital nerve swelling Endocrine system Hypophysitis and thyroiditis Others Prostatitis, mastitis, mediastinitis, pericarditis, and skin (nodules and papules) Reprinted from Saeki T and Kawano M. (2014). IgG4-related kidney disease. Kidney Int., 85(2), 251–7. Copyright © 2014 International Society of Nephrology, with permission from Elsevier. the kidney being the organ in the body with the most pronounced damage in view of the combination of exposure to highly concen- trated, renally excreted toxins and dehydration in situations of pro- fuse sweating and low fluid intake in hot working conditions, when the kidney is working at maximal concentrating capacity for almost 12 h/day. Genetic susceptibility could be a conditioning factor. Other factors are contributing to this cascade of events that make individuals in these communities particularly vulnerable to possible prior kidney damage. Those are low birth weight, malaria, hyperten- sion, diabetes, obesity, smoking habit, excessive alcohol consump- tion, and use of NSAIDs and nephrotoxic medicinal plants. This hypothesis gives a broader range to public health consider- ations and action, since it puts more emphasis on determinants that are both social (economic and social vulnerability of entire farming communities) and environmental (use and abuse of agrochemicals with little or no enforcement of existing internationally accepted re- gulations), with attention also paid to labour rights in the context of occupational health and safety.

Prevention Common themes among the many recommendations made are the ur- gent need for more clearly focused biological–epidemiological–social research programmes. Different groups agree on a holistic approach to this most likely preventable disease. Although science has not yet pro- vided conclusive answers to aetiology, the hypothesized causal factors (particularly toxins) are potentially preventable, and there is scope for action on social and environmental determinants, workplace health and safety, health promotion at individual and community levels, early detection, and timely treatment. Surveillance systems must be re- inforced to assess CINAC trends and intervention impacts. IgG4-related kidney disease IgG4-related disease (IgG4-RD) is a recently recognized clinico pathological entity characterized by a dense lymphoplasmacytic infiltrate that is rich in IgG4-positive plasma cells with fibrosis, and usually an elevated serum IgG4 concentration. The condi- tion was first described in relation to the pancreas, but is now con- sidered to encompass various multiorgan inflammatory conditions (Table 21.9.2.2). IgG4-related kidney disease refers to any form of renal involve- ment by IgG4-RD, with the most common renal manifestation being IgG4-related tubulointerstitial nephritis, which presents as acute or chronic renal insufficiency, renal mass lesions, or both, detectable by renal imaging (contrast CT scan). Pathogenesis Although several mechanisms, including autoimmunity, allergy, or innate immunity, have been discussed, the role of IgG4 in IgG4-RD and the pathogenesis of IgG4-RD is poorly understood. Predominance of a Th2-cell response and activation of regulatory T cells at affected sites have been commonly confirmed in various or- gans in association with IgG4-RD. Production of interleukin (IL)-4, IL-10, and transforming growth factor-β (TGFβ) is also markedly increased in IgG4 tubulointerstitial nephritis compared with other types of tubulointerstitial disease. Pathology In the kidney, the dominant feature associated with IgG4-RD is plasma cell-rich tubulointerstitial nephritis with increased IgG4- positive plasma cells and fibrosis. A unique and characteristic ap- pearance is IgG4-storiform fibrosis, with an irregularly whorled pattern (somewhat resembling that of a straw mat) of nests of in- flammatory cells with irregular fibres surrounding them. This is usually revealed by periodic acid–methenamine silver staining, with the term ‘bird’s-eye fibrosis’ coined because it resembles the ‘bird’s eye’ grain pattern of maple wood (Fig. 21.9.2.7). Various glomerular lesions, most commonly membranous nephropathy, are also reported concurrently with tubulointerstitial nephritis. Several radiological lesions within the kidney are diagnostic for IgG4-RD affecting the kidney in the setting of extrarenal Fig. 21.9.2.7 Characteristic bird’s-eye pattern (periodic acid–methenamine silver stain, magnification ×400). Nests of inflammatory cells with irregular fibres surrounding them. Reproduced with permission from Tang X et al. (2015). Evaluation of diagnostic criteria for IgG4-related tubulointerstitial nephritis. Diagn Pathol, 10, 83. Copyright © Tang et al. 2015.

 biopsy-diagnosed IgG4-RD. These renal lesions include small, low- attenuation lesions (typically bilateral and multiple, found in 65% of patients), significantly enlarged kidneys (20–30%), or tumour masses. The term ‘IgG4-related kidney disease’ has been proposed as a comprehensive term for the renal lesions associated with IgG4.
Clinical features IgG4-RD mainly affects middle-aged to elderly men, many of whom have allergic conditions. Patients with IgG4-RD often have lesions in several organs, with the salivary glands, lacrimal glands, lymph nodes, and pancreas being frequently affected. Systemic symptoms are relatively mild, and renal involvement usually be- comes clinically apparent when renal dysfunction and/or renal radiographic abnormalities are detected, either during systematic examination for extrarenal IgG4-RD or by chance. Oedema may be evident in patients with IgG4-related kidney disease accompanied by glomerular lesions, or in patients with hydronephrosis due to

retroperitoneal fibrosis. Polyclonal hypergammaglobulinaemia is a characteristic feature. Almost all patients with IgG4-related kidney disease have an elevated serum IgG4 level, and 90% have an elevated serum total IgG level. Hypocomplementaemia and a high serum IgE level are characteristic, and eosinophilia is often evident. Although antinuclear antibodies and rheumatoid factors are often positive, anti-DNA, anti-SS-A, anti-SS-B, anti- Sm, and anti-RNP antibodies are usually negative. Proteinuria when present (±50%) is usually mild, but nephrotic-range proteinuria may occur when membranous nephropathy is present. Progressive renal damage may occur, varying from subacute to slowly progressive. Diagnosis and treatment Diagnostic criteria for IgG4 tubulointerstitial nephritis and a diag- nostic algorithm using a set of diagnostic criteria for IgG4-related kidney disease were proposed by a group from North America and the Japanese Society of Nephrology. As a mandatory criterion, they propose a renal histology picture rich in IgG4-positive plasma cells (i.e. >10 IgG4+ plasma cells/high power field in the most concen- trated fields). At least one other feature based on imaging, serology (an elevated serum IgG4 or total IgG level), or IgG4-related involve- ment of another organ is required. An increase in the number of IgG4-positive plasma cells may be a feature of myeloperoxidase– antineutrophil cytoplasmic antibody-associated vasculitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, multicentric Castleman’s disease, lymphoproliferative disorders including malignant lymphoma, and some inflammatory conditions. IgG4 tubulointerstitial nephritis has a quick and favourable re- sponse to corticosteroid therapy, with the usual therapy being oral administration of prednisolone (0.6 mg/kg per day) as induction therapy for 2 to 4 weeks, with the dose then gradually tapered to a low-maintenance dose and continued for several years. Rapid recovery towards normal renal function is seen in most cases, but irreversible renal failure requiring maintenance haemo- dialysis can occur in patients with advanced renal damage before treatment. Relapse may occur in 20% of treated patients. The inci- dence of malignancy in patients with IgG4 tubulointerstitial neph- ritis is 3.5 times higher than that of the general population. Lithium Lithium is used extensively in the treatment of patients with manic- depressive psychosis. Different forms of renal effects/injury have been described, most frequently nephrogenic diabetes insipidus, but also renal tubular acidosis, chronic interstitial nephritis, nephrotic syndrome, and focal segmental glomerular sclerosis/global glom- erular sclerosis. Hyperparathyroidism is also observed in patients treated with lithium. Pathogenesis and pathology Lithium is eliminated from the body almost entirely by the kidney, being filtered at the glomerulus and reabsorbed in the proximal tu- bule, resulting in a clearance of one-third of the normal creatinine clearance. It moves in and out of cells only slowly and accumulates in the kidney, particularly in the collecting tubule, entering these cells through sodium channels in the luminal membrane. Hence, its principal toxicity relates to distal tubular function, where inhibition of adenylate cyclase and generation of cyclic AMP result in down-regulation of aquaporin-2, the collecting tubule water channel, and a decrease in antidiuretic hormone receptor density, leading to re- sistance to antidiuretic hormone. Further effects compound this. A low intracellular level of cyclic AMP leads to the increased cel- lular levels of glycogen observed in kidney biopsy specimens from patients taking lithium, as does the fact that lithium also directly inhibits enzymes involved in glycogen breakdown. The ensuing in- creased glycogen storage may interfere with distal tubular function and be responsible for the observation that polyuria and polydipsia in lithium-treated patients is due to nephrogenic diabetes insipidus. The tubular defect in the distal nephron can also impair the ability to maximally acidify the urine. A lithium-induced decrease in the activity of the H+-ATPase pump in the collecting tubule may be re- sponsible for this defect. Lithium treatment has been aetiologically related to parathyroid hypertrophy and hyperfunction, the latter seeming to be due to an up- ward resetting of the level

at which the plasma calcium concentration depresses parathyroid hormone release. Persistent hypercalcaemia (in 5–10% of the patients) may exacerbate both the concentrating defect and the interstitial nephritis seen in lithium-treated patients. Recently large dysmorphic lysosomes were found in the proximal tubular cells of 8 patients under chronic lithium treatment perfectly comparable with the abnormal lysosomes found in CINAC patients. Renal biopsies from patients taking lithium show a specific histo- logical lesion in the distal tubule and collecting duct. On light mi- croscopy there is swelling and vacuolization in cells associated with a considerable accumulation of periodic acid–Schiff-positive glycogen. This is present in all renal biopsies from patients taking lithium, appears within days after the administration of lithium, and disappears when lithium ingestion is ceased. Hestbech and colleagues were the first to suggest that progres- sive chronic interstitial lesions occurred in the kidneys of patients receiving lithium. However, a controlled study showed no dif- ference between biopsies from patients taking lithium and those from a group of patients who had affective disorders but were not doing so. Specifically, there was no difference in the incidence of glomerular sclerosis, interstitial fibrosis, tubular atrophy, cast for- mation, or interstitial volume, but there was a significant increase

section 21 Disorders of the kidney and urinary tract 4968 in the number of microcysts in the lithium-treated patients. One reason why it has been difficult to determine the nature of lithium-induced chronic renal damage has been the lack, until recently, of an animal model in which lesions similar to those noted in human biopsies could be demonstrated. However, a recent study on lithium nephrotoxicity carried out in the rabbit showed clear-cut evidence of progressive histological and functional impairment, with the de- velopment of significant interstitial fibrosis, tubular atrophy, glom- erular sclerosis, and cystic tubular lesions. A recent publication by Markowitz and colleagues revealed chronic tubulointerstitial neph- ropathy in 100% of 24 patients who had received lithium for sev- eral years, associated with cortical and medullary tubular cysts or dilatation. There was also a surprisingly high prevalence of focal segmental glomerulosclerosis and global glomerulosclerosis, some- times of equivalent severity to the chronic tubulointerstitial disease. Despite discontinuing lithium treatment, seven of nine patients with initial serum creatinine values above 2.5 mg/dl (225 µmol/litre) pro- gressed to endstage renal disease. A French follow-up study of lithium-treated patients demon- strated that the duration of lithium therapy and the cumulative dose of lithium were the major determinants of nephrotoxicity and estimated a prevalence of lithium-related endstage renal failure in 2 of 1000 dialysis patients. Twelve out of 74 patients in this study reached endstage renal failure at a mean age of 65 years, with an average latency between onset of lithium therapy and endstage renal failure of 20 years. Lepkifker and colleagues retrospectively studied 114 subjects with major depressive or schizoaffective disorders who had been taken lithium for 4 to 30 years from 1968 to 2000. Long- term lithium therapy did not influence glomerular function in most patients, but 20% of those receiving long-term lithium exhibited ‘creeping creatinine’ and developed chronic renal insufficiency. Clinical features Apart from acute lithium intoxication, chronic poisoning can occur in patients whose lithium dosage has been increased or in those with a decreased effective circulating volume, decreased sodium intake, diabetes mellitus, gastroenteritis, and renal failure, thereby resulting in an increase in serum lithium levels. Symptoms associated with poisoning include lethargy, drowsiness, coarse hand tremor, muscle weakness, nausea, vomiting, weight loss, polyuria, and polydipsia. Severe toxicity is associated with increased deep tendon reflexes, seizures, syncope, renal insufficiency, and coma. The commonest manifestation is altered mental status. Chronic lithium poisoning is frequently associated with electro- cardiographic changes, including ST-segment depression and in-

verted T waves in the lateral precordial leads. Lithium is concentrated within the thyroid and inhibits the synthesis and release of thyroxine, which can lead to hypothyroidism, and it may also cause thyrotoxi- cosis. Symptoms of hypercalcaemia may also be present, exacerbating the urinary concentrating defect already present in these patients. In patients with glomerular lesions such as minimal-change or focal glomerular sclerosis, proteinuria generally begins within 1.5 to 10 months after the onset of therapy, completely or partially re- solving in most patients within 4 weeks after lithium is discontinued. Reinstitution of lithium has led to recurrent nephrosis in some cases. The hyperparathyroidism observed in patients receiving lithium treatment is characterized by elevated parathyroid hor- mone levels, hypercalcaemia, hypocalciuria, and normal serum phosphate levels, in contrast to primary hyperparathyroidism in which hypophosphataemia and hypercalciuria are seen. Diagnosis and treatment The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5–2.0 mmol/litre), moderate (2.0–2.5 mmol/litre), or severe (>2.5 mmol/litre). Polyuria and polydipsia due to nephrogenic diabetes insipidus and other acute manifestations of the effect of lithium on the kidney usually disappear rapidly if lithium is withdrawn. The decision about management, however, usually revolves around the relative benefit of the lithium in controlling and preventing the manifestation of manic-depressive psychosis, and the disadvantage to the patient of the major side effect of lithium, that is, polyuria. In most cases, the lithium is so clearly beneficial that the polyuria is accepted as a side effect and treatment continued. It is likely that the serum concen- tration of lithium is important, and that renal damage is more prob- able if the serum concentration is consistently high, or if repeated episodes of lithium toxicity occur. The serum lithium concentration should therefore be monitored carefully (at least every 3 months) and maintained at the lowest level that will provide adequate control of psychiatric symptoms. Much more difficult to handle is the situation where a patient on long-term lithium therapy is found to have impaired renal function for which there is no obvious alternative cause. As stated earlier, renal failure may progress even if lithium therapy is withdrawn, and in some patients the discontinuation of lithium can lead to a devastating deterioration in their psychiatric condition. The deci- sion as to whether or not to discontinue lithium should therefore be made after frank and open discussion, admitting all uncertainties, with the patient, psychiatric colleagues, and (if appropriate) rela- tives/carers. Radiation nephropathy Radiation nephropathy is a renal disorder caused by ionizing ra- diation. The kidney may be injured by radiation administered to tumours within the kidney or nearby tissues (testis, ovary, retroperitoneum). Clinicians were aware of the potential adverse ef- fects of radiography on renal function from the beginning of the 20th century, and between 1940 and 1960 a significant number of cases were reported. In 1953, Luxton established the clinical features of the condition and defined the tolerance of the kidney to irradiation, leading to preventive shielding of the kidneys in patients receiving radiation therapy and to a marked decline in the frequency of radi- ation nephropathy. In recent years, however, total body irradiation preceding bone marrow transplantation has resulted in an increasing incidence of radiation nephropathy, with late chronic renal failure developing in 20% of patients who receive this treatment. Pathogenesis and pathology The radiation doses traditionally associated with radiation neph- ropathy were above 2000 rad (20 Gy) (less in children). By contrast, in patients receiving total body irradiation preceding bone marrow transplantation, renal impairment was observed after doses of 1000 to 1400 rad (10–14 Gy). Fractionation, time, and effects of cytotoxic

 chemotherapy can probably explain the differences. In laboratory rodents, fractionation of the total dose into multiple separated doses decreases the

risk, probably due to repair of sublethal radiation damage during the time between the fractionated doses. Total body irradiation before bone marrow transplantation is usually adminis- tered over a short period, which does not allow sufficient time for the repair of radiation injury to the kidney. Moreover, the additional cytotoxic chemotherapy given to these patients potentiates the ef- fects of ionizing radiation. The precise pathogenesis of radiation nephropathy remains to be determined. The initial target of ionizing radiation within the kidney appears to be the endothelial cell. Radiation kills cells by damaging DNA, so that cell death after radiation is delayed until the cell divides. After the initial glomerular endothelial injury, vascular occlusion subsequently develops, leading to tubular at- rophy. Because inflammatory cells are not seen in the renal paren- chyma, the previously used terminology of 'radiation nephritis' is a misnomer. The pathological features of radiation nephropathy comprise a continuous spectrum of changes that vary in relation to the dose of irradiation administered and the time elapsed after exposure. Large doses are followed by complete atrophy, thickening of basement membranes, and interstitial fibrosis. Clinical features Radiation nephropathy can take several forms. Acute radiation nephropathy occurs between 6 and 12 months after radiation therapy and presents with hypertension, anaemia, and oedema. The severity of hypertension ranges from mild to malignant, and more than one-half of the patients progress to chronic renal failure. Radiation nephropathy after total body irradiation before bone marrow transplantation most closely corresponds to this acute form of radiation nephropathy. A more insidious chronic form of radiation nephropathy develops over a period of several years and presents primarily with diminished glomerular filtration rate, hypertension, and (occasionally) protein- uria. Another subset of patients may develop hypertension within a few years of irradiation, evolving in some to malignant hyperten- sion with accelerated loss of renal function. Isolated persistent or intermittent proteinuria may also occur, frequently developing more than a decade after radiation exposure. Diagnosis and treatment Radiographic studies may help in the diagnosis of acute radiation nephropathy. CT scans with contrast demonstrate sharply de- marcated, dense, persistent nephrograms corresponding to the irradiated areas. The treatment of radiation nephropathy is supportive. Aggressive treatment of hypertension may slow the progression of renal disease, and the use of angiotensin-converting enzyme inhibitors may have its classic renoprotective effect independent of antihypertensive action. Hypertension due to unilateral disease may respond to nephrectomy. Since radiation nephropathy is an irreversible process, preventive measures should be taken during the administration of radiation. This includes selective shielding of the kidneys and the use of frac- tionated doses. Patients exposed to additional nephrotoxins remain at an increased risk of toxic effects. Toxins Lead Lead toxicity affects many organs, resulting in encephalopathy, an- aemia, peripheral neuropathy, gout, and renal failure. It was the epi- demic of lead nephropathy in Queensland (Australia) that provided the strongest link between lead and chronic tubulointerstitial neph- ritis. Henderson noted an excess mortality due to chronic interstitial nephritis in Queensland but not in other parts of Australia, and cor- related the incidence of granular contracted kidneys at autopsy with the lead content of the skull in people from Queensland and Sydney, showing that this correlated closely with the incidence of renal failure. Exposure was due to the lead-based paints used between 1890 and 1930, but recently the source of lead is industrial exposure. This type of exposure is often insidious and occurs over a very long period. Two studies have shown an inverse relationship between low-level lead exposure and renal function in the general population. Recent studies have failed to show any effect on renal function 17 to 50 years after an episode of acute childhood plumbism, the difference with Henderson's findings reflecting the greater lead burden in his study compared to the recent ones. Although low-level lead exposure in the general population is associated with mild but significant

depression of renal function, in particular in patients with hypertension, its role in the development of endstage renal disease is unclear. Pathogenesis and pathology The pathogenesis of renal disease seen in the context of lead exposure may be related to proximal tubule reabsorption of filtered lead, with subsequent accumulation in proximal tubule cells. Aminoaciduria, glycosuria, and phosphaturia representing Fanconi's syndrome are observed after lead exposure, and thought to be related to an effect of lead on mitochondrial respiration and phosphorylation. Since lead is also capable of reducing 1,25-dihydroxyvitamin D synthesis, prolonged hyperphosphaturia and hypophosphataemia caused by lead poisoning in children could result in bone demineralization and rickets. Chronic lead poisoning can affect glomerular func- tion. After an initial period of hyperfiltration, the glomerular filtra- tion rate is reduced and nephrosclerosis and chronic renal failure may ensue. Protracted lead exposure also interferes with the distal tubular secretion of urate, leading to hyperuricaemia and gout. Other pathophysiological mechanisms include the induction of oxi- dative stress and generation of free radicals, which in turn may result in high blood pressure, inflammation, apoptosis, and, ultimately, de- velopment of chronic renal lesions. Renal biopsies in patients with subclinical lead nephropathy and a mild to moderate decrease in glomerular filtration rate primarily show focal tubular atrophy and interstitial fibrosis with minimal cellular infiltration. Electron microscopy shows mitochondrial swelling, loss of cristae, loss of basal infoldings, and a lysosomal-like structure containing dense bodies (not comparable to the lysosomal lesions observed in CINAC patients) in the proximal tubular cells. In Australian patients who died as a result of severe lead exposure, their kidneys were fibrotic and shrunken, the interstitium showed variable degrees of fibrosis with tubular dilatation, and the vessels had thickened muscular walls with subintimal hyaline deposition in afferent arterioles, but these findings in patients with endstage renal failure were nonspecific.

section 21 Disorders of the kidney and urinary tract 4970 Clinical features Renal failure becomes apparent years after exposure and is asso- ciated with gout in most, if not all, cases. Hypertension is also a very common feature of lead nephropathy, and an association be- tween hypertension without renal failure and low-level lead ex- posure has gained increasing recognition in recent years. Although hyperuricaemia is common in renal failure, gout is less so and its presence should raise the possibility of lead nephropathy. However, whether chronic lead nephropathy exists as a clinical entity has been questioned. Many studies of occupational lead poisoning have not taken into account the coexposure to other toxins such as cadmium. Additionally, the relationship between early markers of renal tubular dysfunction, such as the urinary excretion of low molecular weight proteins or N-acetyl β-d-glucosaminidase, to the subsequent devel- opment of renal failure remains to be determined. Diagnosis and treatment The diagnosis of lead nephropathy should be considered in any pa- tient with progressive renal failure, mild to moderate proteinuria, significant hypertension, a history of gout, and an appropriate his- tory of exposure. As the blood lead level only reflects recent lead exposure, and is usually normal in patients with chronic renal failure due to their pre- viously sustained low-level lead exposure, the diagnosis has to be based on measurement of the body lead burden. The test of choice is the ethylenediaminetetraacetic acid (EDTA) mobilization test. This involves the administration of 2 g of EDTA intramuscularly in two divided doses 8 to 12 h apart, and collection of three consecutive 24-h urine samples. A cumulative excretion of more than 600 µg is suggestive for a high body lead burden. Renal failure in itself does not increase body lead load but it does delay the excretion of lead. There is very little experience of the therapeutic use of EDTA in patients with chronic renal failure. Wedeen and colleagues treated eight industrially exposed patients with EDTA injections three times weekly for 6 to 15 months, all

having mild renal failure with glom- erular filtration rates of around 50 ml/min before treatment; four patients improved with a 20% increase in their glomerular filtration rate. Results from studies in Taiwan indicate that low-level environ- mental lead exposure accelerates progressive diabetic nephropathy as well as CKD in patients without diabetes, and that repeated che- lation therapy may improve renal function and slow the progression of renal insufficiency. Cadmium Cadmium is a cumulative environmental pollutant and accumulates in the human body after inhalation or gastrointestinal absorption. Due to its various applications and increased industrial production, it has been released into the environment in much larger amounts from the 1950s onwards, particularly in Belgium and Japan, which are among the most important cadmium-producing countries worldwide. However, the atmospheric emissions of cadmium from zinc smelters have been reduced since the 1970s. Currently, normal cadmium values are set at 0.1 to 0.8 µg/litre (nonsmokers) in blood, and 0.02 to 0.7 µg/g creatinine in urine. Cadmium is a highly toxic metal and it has long been recognized that high-level exposure after inhalation or ingestion can give rise to nephrotoxicity, and that this effect is usually considered to be the earliest and most important feature from the point of view of health. When exposed to high levels of cadmium in the workplace (cad- mium in renal cortex >100–400 µg/kg wet weight), workers have developed tubular proteinuria, renal glycosuria, aminoaciduria, hypercalciuria, phosphaturia, and polyuria, and in a few severe cases (long-standing high exposure and urinary excretion >20 µg/g cre- atinine and β2-microglobulin >1500 µg/g creatinine), renal damage may progress to an irreversible reduction in glomerular filtration. Signs of distal tubular damage such as a cadmium-induced inhib- ition of antidiuretic hormone-stimulated ion transport have also been reported. The extent to which chronic low-level environmental exposure to cadmium affects renal function is much less clear. The Cadmibel study, in which a random sample of 1699 subjects was recruited from four areas of Belgium with varying degrees of cadmium pol- lution, showed that (after standardization for several confounding factors) five markers of renal dysfunction (retinol binding protein, N-acetyl-β-glucosaminidase, β2-microglobulin, amino acids, and calcium) were significantly associated with urinary cadmium ex- cretion. There was a 10% probability of these variables being ab- normal when urinary cadmium levels exceeded 2 to 4 µg/24 h. However, in a 5-year follow-up of a subcohort from the Cadmibel study, the so-called Pheecad study, in which 593 individuals with the highest urinary cadmium excretion were re-examined on average 5 years later, it was demonstrated that the subclinical tubular effects previously documented were not associated with deterioration in glomerular filtration rate. Hence, in the envir- onmentally cadmium-exposed population, the renal effects due to cadmium appear to be weak, stable, and even reversible. These findings in environmentally exposed subjects may reasonably be extrapolated to the current, moderately exposed, occupational population, where, in various epidemiological studies, increased cadmium levels/exposure have repeatedly been associated with disturbed levels of markers of early renal dysfunction, but without evidence for accelerated progression towards chronic renal failure. Recent findings point to the importance of coexposure as it was shown that moderate occupational lead exposure increases the renal response to low levels of cadmium as indicated by the in- creased strength of the association between cadmium in blood and urine and early renal biomarkers of dysfunction (i.e. N-acetyl- β-glucosaminidase, intestinal alkaline phosphatase, and retinol binding protein). Other studies reported that the presence of dia- betes, increased levels of tissue antimetallothionein-1 antibodies, and/or concomitant exposure to organic arsenic, also hold an in- creased risk for cadmium-induced renal dysfunction. There is no specific treatment for cadmium-induced renal disease, other than supportive care and change of residence area, to avoid further excessive cadmium exposure. Metabolic disorders Chronic hypokalaemia Several renal

abnormalities, most of which are reversible with po- tassium repletion, can be induced by hypokalaemia. Vasopressin- resistant impairment of the ability to concentrate the urine, increased renal ammonia production, enhanced bicarbonate reabsorption,

21.9.2 Chronic tubulointerstitial nephritis 4971 altered sodium reabsorption, and hyperkalaemic nephropathy have all been described. Persistent hypokalaemia can induce a variety of changes in renal function, impairing tubular transport and possibly inducing chronic tubulointerstitial disease and cyst formation. Hypokalaemic neph- ropathy in humans produces characteristic vacuolar lesions in the epithelial cells of the proximal tubule and (occasionally) the distal tubule, abnormalities which probably require about 1 month to develop. More severe changes occur if prolonged hypokalaemia is maintained, including interstitial fibrosis, tubular atrophy, and cyst formation that is most prominent in the renal medulla. The patho- genesis of these changes is not well understood. Renal growth accelerates when rats are placed on a potassium- deficient diet, and within 8 days there is a 25% increase in kidney mass. The changes are most prominent in the outer medulla, es- pecially the inner stripe, where hyperplastic enlarged collecting duct cells form cellular outgrowths that project into the lumen causing partial obstruction. If the potassium-deficient state per- sists, then cellular infiltrates appear in the renal interstitial com- partment and tubulointerstitial fibrosis develops. It has been proposed that some of these pathological changes may be ini- tiated by the high levels of ammonia generated in potassium- deficiency states and may be mediated through the activation of the alternate complement pathway. In support of this hypothesis is the finding that bicarbonate supplementation sufficient to sup- press renal ammoniagenesis attenuates the renal enlargement and tubulointerstitial disease: against it are reports that increased renal ammoniagenesis induced by acid loading causes renal enlarge- ment without cellular proliferation or interstitial disease. A recent paper provides results consistent with a sustained role for insulin- like growth factor-1 (IGF-1) in promoting the marked tubular epi- thelial cell hypertrophy and hyperplasia that occurs in the inner stripe of the outer medulla of the kidney with chronic potassium depletion. The same study also showed that potassium depletion causes a selective increase in the renal expression of TGFβ in the hypertrophied nonhyperplastic thick ascending limb, but, unlike IGF-1, it is absent from the hyperplastic collecting duct cells. This might be responsible for preventing the conversion of the mito- genic stimulus of IGF-1 into a hypertrophic one. It is possible that TGFβ causes the prominent interstitial infiltrate that develops in chronic hypokalaemia, since this growth factor is a well-known chemoattractant for macrophages. A study has shown that angiotensin receptor blockade ameliorates tubulointerstitial injury induced by chronic potassium deficiency, and the same authors also showed that endothelin-1 can mediate hypokalaemic renal injury in two different ways, by directly stimu- lating endothelin-A receptors and by locally promoting endogenous endothelin-1 production via endothelin-B receptors, hence endothelin-A and -B receptor blockade may be renoprotective in hypokalaemic nephropathy. Hyperoxaluria Hyperoxaluria may be primary or acquired. The primary form is a rare inherited disorder due to an enzymatic abnormality in the metabolism of glyoxylic acid. The acquired forms of hyperoxaluria are more common and result either from the ingestion of oxalate precursors, such as ethylene glycol and ascorbic acid, and exposure to methoxyflurane anaesthesia, or from increased absorption from the intestinal tract in those with inflammatory bowel disease or who have undergone small-bowel resection. Oxalate is the salt forming ion of oxalic acid, which is widely distributed in both plants and animals. Oxalic acid may form ox- alate salts with various cations, such as sodium, potassium, mag- nesium, and calcium. Although sodium oxalate, potassium oxalate, and magnesium oxalate are water soluble, calcium oxalate is nearly

insoluble. Excretion of oxalate occurs primarily by the kidneys via glomerular filtration and tubular secretion. Since ox- alate can bind with calcium in the kidney, increased urinary ox- alate excretion (hyperoxaluria) leads to urinary calcium oxalate supersaturation, resulting in the formation and putative retention of calcium oxalate crystals in renal tissue. This first occurs in the proximal tubules, where oxalate is secreted, and these calcium ox- alate crystals may contribute to the formation of diffuse renal cal- cifications (nephrocalcinosis) and renal stones (nephrolithiasis, of which c.75% are predominantly composed of calcium oxalate) (see Chapter 21.14). If the overload is insidious and chronic, then inflam- matory cell infiltration, oedema, interstitial fibrosis, tubular atrophy, and dilatation result in chronic tubulointerstitial nephritis with progressive renal failure. Up to now, many (if not all) preventive or therapeutic strategies fail in their compliance or effectiveness, hence stone recurrence is still very common. Recently, experimental data in a rat model of secondary hyperoxaluria has provided evidence that lanthanum carbonate can efficiently bind oxalate in the intestine and decrease nephrocalcinosis. Clinical confirmation is needed, but lanthanum carbonate might be a promising therapy for secondary hyperoxaluria. Hypercalcaemia Prolonged elevation of urinary and serum calcium levels may re- sult in the deposition of calcium in the kidney, which also occurs in some clinical conditions not associated with hypercalcaemia. Calcium is most concentrated in the medulla, where degeneration and tubular necrosis begins due to intracellular overload, with damage to mitochondria and other critical organelles. Reactive in- flammatory changes occur in the adjacent interstitium, and necrotic cells may cause intratubular obstruction and tubular atrophy. The final results of these changes are focal areas of tubular atrophy, inter- stitial fibrosis, and a mononuclear cell infiltrate. See Chapter 21.14 for further discussion. Hyperuricaemia/hyperuricosuria There are three different types of renal disease induced by abnormal uric acid metabolism: acute uric acid nephropathy, chronic urate nephropathy, and uric acid stone disease, the last being discussed in Chapter 21.14. The kidneys are mainly responsible for the excretion of uric acid and are a primary target organ affected in disorders of urate metab- olism. Renal lesions result from the crystallization of uric acid either in the urinary outflow tract or in the renal parenchyma. The deter- minants of uric acid solubility are its concentration and the pH of the medium in which it is dissolved, hence the supersaturation of fluid within the renal tubules as excreted uric acid becomes concentrated in the medulla, and the acidification of the urine in the distal tubule, are both conducive to the precipitation of uric acid. The major sites of urate deposition are the renal medulla, the collecting tubules, and the urinary tract. The pKa of uric acid is 5.7, and at the acid pH of

 the fluid in the distal tubule the bulk of filtered urate will be present in its nonionized form as uric acid, whereas at the more alkaline pH of the blood and interstitium it is in its ionized form as urate salts. Acute uric acid nephropathy Acute uric acid nephropathy is an uncommon condition caused by the precipitation of birefringent uric acid crystals in the col- lecting tubules, with consequent tubular obstruction, dilatation, and inflammation. This can occur in disorders associated with an increased production of uric acid (e.g. myeloproliferative or lymphoproliferative disorders, tumour lysis syndrome, chronic haemolytic anaemia, psoriasis, or the Lesch–Nyhan syndrome) or when there is increased renal clearance of uric acid (e.g. inherited or acquired defects of tubular urate transport or uricosuric drugs). In those prone to acute uric acid nephropathy, management centres on prophylaxis with a plentiful fluid intake, with or without alkalinization of the urine, and pretreatment with allopurinol or recombinant urate oxidase enzyme (rasburicase). Presentation of acute uric acid nephropathy is with acute kidney injury, with urine microscopy revealing plentiful birefringent crystals. Chronic

urate nephropathy The principal renal lesion in chronic hyperuricaemia is the depos- ition of microtophi of amorphous urate crystals in the interstitium, with a surrounding giant cell reaction. This results in a sec- ondary chronic inflammatory response similar to that seen with microtophus formation elsewhere in the body, potentially leading to interstitial fibrosis and chronic renal failure. Uric acid is an independent risk factor for cardiovascular death and major clinical events. Hyperuricaemia induces endothelial dys- function, and uric acid regulates critical proinflammatory path- ways in vascular smooth muscle cells, possibly having a role in the vascular changes associated with hypertension and vascular dis- ease. It also accelerates renal progression in the remnant kidney model via a mechanism linked to high systemic blood pressure and cyclooxygenase-2 (COX-2)-mediated thromboxane-induced vas- cular disease. These studies provide direct evidence that uric acid may be a true mediator of renal disease and progression, but clinical evidence linking chronic renal failure to gout is weak, and the long- standing notion that chronic renal disease is common in patients with hyperuricaemia has been questioned in the light of prolonged follow-up studies of renal function in people with this condition. Renal dysfunction could be documented only when the serum urate concentration was more than 10 mg/dl (600 µmol/litre) in women and more than 13 mg/dl (780 µmol/litre) in men for prolonged periods. Furthermore, the deterioration of renal function in those with hyperuricaemia of a lower magnitude has been attributed to the higher than expected occurrence of hypertension, diabetes mellitus, abnormal lipid metabolism, and nephrosclerosis. Nonetheless, it seems reasonable to prescribe allopurinol (in a dose appropriate to the level of renal function) to those very rare patients with bi- opsy evidence of ‘gouty nephropathy’, and possibly to patients with chronic renal failure who have a grossly elevated serum urate. There is an association between severe lead intoxication, chronic renal failure, and gout (saturnine gout) (see earlier discussion). It has also been suggested that there might be an association between renal disease and hyperuricaemia in those with a past history of ex- posure to lead and consequent subclinical lead toxicity (saturnine nephropathy). Evidence for this association is not clear cut, nor is the mechanism whereby lead exposure might aggravate hyperuricaemia and renal failure. FURTHER READING Sarcoidosis Kettritz R, et al. (2006). The protean face of sarcoidosis revisited. Nephrol Dial Transplant, 21, 2690–4. Korzets Z, et al. (1985). Acute renal failure due to sarcoid granuloma- tous infiltration of the renal parenchyma. Am J Kidney Dis, 6, 250–3. Analgesic nephropathy Blohme I, Johansson S (1981). Renal pelvic neoplasms and atyp- ical urothelium in patients with end-stage analgesic nephropathy. Kidney Int, 20, 671–5. Chang SH, Mathew TH, McDonald SP (2008). Analgesic nephropathy and renal replacement therapy in Australia: trends, comorbidities and outcomes. Clin J Am Soc Nephrol, 3, 768–76. De Broe M, Elseviers, MM (1998). Analgesic Nephropathy. New England Journal Of Medicine, 338(7), 446–52. De Broe ME, Elseviers MM (2009). Over-the-counter analgesic use. J Am Soc Nephrol, 20, 2098–103. Duggin GG (1996). Combination analgesic-induced kidney dis- ease: the Australian experience. Am J Kidney Dis, 28 Suppl 1, S39–47. Fored CM, et al. (2001). Acetaminophen, aspirin, and chronic renal failure. N Engl J Med, 345, 1801–8. Henrich WL, et al. (2006). Non-contrast-enhanced computerized tomography and analgesic-related kidney disease: report of the na- tional analgesic nephropathy study. J Am Soc Nephrol, 17, 1472–80. Ibanez L, et al. (2005). Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. Kidney Int, 67, 2393–8. Mihatsch MJ, Khanlari B, Brunner FP (2006). Obituary to analgesic nephropathy: an autopsy study. Nephrol Dial Transplant, 21, 3139–45. Mihatsch MJ, et al. (1983). Capillary sclerosis of the urinary tract and analgesic nephropathy. Clin Nephrol, 20, 285–301. Perneger TV, Whelton PK, Klag MJ (1994). Risk of kidney failure as- sociated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory

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