Toxic Nephropathies

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Tubular interstitial structures of the kidney are particularly vulnerable in face of toxic compounds. High concentration of the toxics in the medulla as well as medullary hypoxia and renal hypoperfusion could explain this particularity. Clinical nephrotoxicity involves toxins of diverse origin. The culprits are often registered and non registered drugs either prescribed or purchased over the counter. Other major causes result from occupational and industrial exposures. Sometimes, the identification of the nephrotoxin requires astuteness and long investigations especially in cases of environmental toxins or prolonged intake of unregulated drugs or natural products. A correct diagnosis of the causes is, however, the key for future prevention of renal diseases. The diagnosis of “chronic interstitial nephritis of unknown origin” should, therefore, no longer be used.
Exposure to Nephrotoxins

TOXIC CAUSES OF CHRONIC TUBULOINTERSTITIAL RENAL DISEASES

Metals (Environmental or Occupational Exposure)
- Lead
- Cadmium

Drugs or Additives (Use, Misuse, or Abuse)
- Lithium
- Germanium
- Analgesics
- Cyclosporine
- Mesalazine

Fungus and Plant Toxins (Environmental or Iatrogenic Exposure)
- Ochratoxins
- Aristolochic acids

Exposure to Metals

FIGURE 10-1
Chronic exposure to drugs, occupational hazards, or environmental toxins can lead to chronic interstitial renal diseases. The following are the major causes of chronic interstitial renal diseases: occupational exposure to heavy metals; abuse of over-the-counter analgesics; misuse of germanium; chronic intake of mesalazine for intestinal disorders, lithium for depression, and cyclosporine in renal and nonrenal diseases; and environmental or iatrogenic exposure to fungus or plant nephrotoxins (ochratoxins, aristolochic acids).

FIGURE 10-2
Occupational exposure to metals and risks for chronic renal failure. Comparison of the occupational histories of 272 patients with chronic renal failure with those of a matched control group having normal renal function has shown an increased risk of chronic renal failure after exposure to mercury, tin, chromium, copper, and lead. In this study the increased risk with exposure to cadmium was not statistically significant. Squares indicate odds ratios; circles indicate CIs. (Adapted from Nuyts and coworkers [1]; with permission.)
Lead nephropathy

**CAUSES OF LEAD NEPHROPATHY**

**Environmental**
- Eating paint from lead-painted furniture, woodwork, and toys in children
- Lead-contaminated flour
- Home lead-contaminated drinking water from lead pipes
- Drinking of moonshine whiskey

**Occupational**
- Lead-producing plants: lead smelters, battery plants

**FIGURE 10-3**
Lead nephropathy associated with environmental and occupational exposure. Epidemiologic observations have established the relationship between lead exposure and renal failure in association with children eating lead paint in their homes, chronic ingestion of lead-contaminated flour, lead-loaded drinking water in homes, and drinking of illegal moonshine whiskey [2,3]. Occupational exposure in lead-producing industries also has been associated with a higher incidence of renal dysfunction.

**CLINICAL MANIFESTATIONS OF LEAD NEPHROPATHY**

- Gout
- Arterial hypertension
- Renal failure (interstitial type)

**FIGURE 10-4**
Gout and hypertension are the major clinical manifestations of lead nephropathy. The prominent feature of early hyperuricemia in lead nephropathy may explain the confusion between lead nephropathy and gout nephropathy. Lead urinary excretion after ethylenediamine tetraacetic acid (EDTA)–lead mobilization testing may help with the correct diagnosis [3].

**FIGURE 10-5**
Ethylenediamine tetraacetic acid (EDTA)–lead mobilization test in lead nephropathy. EDTA (calcium disodium acetate) for detecting lead nephropathy. This test consists of a 24-hour urinary lead excretion over 3 consecutive days after administration of 2 g of EDTA by intramuscular route on the first day in divided doses 12 hours apart. Persons without excessive lead exposure excrete less than 0.6 mg of lead during the day after receiving 2 g of EDTA parenterally. In the presence of renal failure, the excretion is delayed; however, the cumulative total remains less than 0.6 mg over 3 days (From Batuman and coworkers [3]; with permission.)

**FIGURE 10-6**
Ethylenediamine tetraacetic acid (EDTA)–lead mobilization test in chronic renal failure of uncertain origin (A–C). In a study of 296 patients without history of lead exposure, the results of this test were abnormal in 15.4% (II) of patients with hypertension and normal renal function and in 56.1% of patients with renal failure of uncertain origin (in 44.1% of the patients without associated gout (III) and in 68.7% of the patients with associated gout (IV), respectively).

(Continued on next page)


Cadmium nephropathy

**FIGURE 10-6 (Continued)**

The EDTA–lead mobilization test was normal in normotensive subjects with normal renal function and in patients with chronic renal failure (I) of well-known origin (V). (Adapted from Sanchez-Fructuoso and coworkers [4].)

**FIGURE 10-7**

Decrease in renal function after 25-year exposure to cadmium (Cd). In workers exposed to cadmium for an average time of 25 years, a progressive decrease in renal function occurs during a 5-year follow-up period, despite removal from cadmium exposure 10 years earlier. On average, the glomerular filtration rate was shown to be decreased to 31 mL/min/1.73 m² after 5 years instead of the expected age-related value of 5 mL/min/1.73 m². (Adapted from Roels and coworkers [5].)

**FIGURE 10-8**

Tubular markers in cadmium workers. Impairment of renal proximal tubular epithelium induced by cadmium can be documented by an increase in urinary excretion of urinary neutral endopeptidase 24.11 (NEP), an enzyme of the proximal tubule brush borders, as well as by an increase in microproteinuria: Clara cell protein (CC16), retinol-binding protein (RBP) and β₂-microglobulin (β₂-m). The data were obtained from 106 healthy persons working in cadmium smelting plants. These markers could be used for the screening of cadmium workers. (Adapted from Nortier and coworkers [6].)
Lithium nephropathy

**LITHIUM NEPHROTOXICITY**

- Reversible polyuria and polydipsia
- Persistent nephrogenic diabetes insipidus
- Incomplete distal tubular acidosis
- Chronic renal failure (chronic interstitial fibrosis)

**FIGURE 10-9**

Lithium acts both distally and proximally to antidiuretic hormone-induced generation of cyclic adenosine monophosphatase. Polyuria and polydipsia can occur in up to 40% of patients on lithium therapy and are considered harmless and reversible. However, nephrogenic diabetes insipidus may persist months after lithium has been discontinued [7]. Lithium also induces an impairment of distal urinary acidification. Chronic renal failure secondary to chronic interstitial fibrosis may appear in up to 21% of patients on maintenance lithium therapy for more than 15 years [8]. However, these observations are still a matter of debate [7].

**FIGURE 10-10** (see Color Plate)

Lithium nephropathy. A 22-year-old female patient was on maintenance lithium therapy (lithium carbonate 750 mg/d) for 5 years. She presented with polyuria (6500 mL/d) and moderate renal failure (creatinine clearance, 60 mL/min). Proteinuria was not present, and the urinary sediment was unremarkable. A renal biopsy showed focal interstitial fibrosis with scarce inflammatory cell infiltrate, tubular atrophy, and characteristic dilated tubule (microcyst formation). Half of the glomeruli (not shown) were sclerotic. (Magnification × 125, periodic acid-Schiff reaction.)

Germanium nephropathy

**CIRCUMSTANCES OF CHRONIC RENAL FAILURE SECONDARY TO GERMANIUM SUPPLEMENTS**

- Ge-dioxyde elixir, food additives, or capsules (used to improve health in normal persons [Japan])
- Ge-lactate-citrate (used to rebuild the immune system) in patients with HIV infection (Switzerland)
- Ge-lactate-citrate (used to improve health) in patients with cancer (the Netherlands)
- Ge-dioxyde elixir (used to restore health) in patients with chronic hepatitis (Japan)

**FIGURE 10-11**

Germanium (atomic number, 32; atomic weight, 72.59) is contained in soil, plants, and animals as a trace metal. It is widely used in the industrial fields because of its semiconductive capacity. The increased use of natural remedies and trace elements to protect, improve, or restore the health has lead regular supplementation with germanium salts either through food addition or by the means of elixirs and capsules. The chronic supplementation by germanium salts was at the origin of the development of chronic renal failure secondary to a tubulointerstitial nephritis [9–12].
10.6 Tubulointerstitial Disease

**FIGURE 10-12**
Light microscopy of renal tissue in a patient with chronic renal failure secondary to the chronic intake of germanium, showing focal tubular atrophy and focal interstitial lymphocyte infiltration. A, Hematoxylin and eosin stain. (Magnification ×162.) Renal tubular epithelial cells show numerous dark small inclusions. B, Periodic acid–Schiff reaction. (Magnification, ×350.) (From Hess and coworkers [12]; with permission.)

### Exposure to Analgesics

**FIGURE 10-13**
Analgesic nephropathy and papillary necrosis. The characteristic feature of analgesic nephropathy is the papillary necrosis process that begins with swollen papillae and continues with fornical erosion, detachment, and calcification of necrotic papillae.

**FIGURE 10-14**
Pathology of analgesic nephropathy. Nephrectomy showing a kidney reduced in size with necrosed and calcified papillae.
Toxic Nephropathies

**FIGURE 10-15**
Radiologic appearance of papillary necrosis in analgesic nephropathy. The pyelogram was obtained by pyelostomy. It shows a swollen papilla (upper calyx), fornical erosion (middle calyx), and detachment of papilla, or filling defect (lower calyx).

**CLINICAL FEATURES OF ANALGESIC NEPHROPATHY**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily consumption of analgesic mixtures</td>
<td>100%</td>
</tr>
<tr>
<td>Women</td>
<td>80%</td>
</tr>
<tr>
<td>Headache</td>
<td>80%</td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>35–40%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>30–48%</td>
</tr>
<tr>
<td>Papillary necrosis (clinical)</td>
<td>20%</td>
</tr>
<tr>
<td>Papillary calcifications (computed tomography scan)</td>
<td>65%</td>
</tr>
</tbody>
</table>

**FIGURE 10-16**
Classic analgesic nephropathy is a slowly progressive disease resulting from the daily consumption over several years of mixtures containing analgesics usually combined with caffeine, codeine, or both. Caffeine and codeine create psychological dependence. Most cases of analgesic nephropathy occur in women. In 80% of the cases, analgesics were taken for persistent headache. Gastrointestinal complaints are also frequent, as are urinary tract infections. Evidence of clinical papillary necrosis (fever and pain) is present in 20% of cases. Calcifications of papillae (detected by computed tomography scan) are present in 65% of persons who abuse analgesics [13].

**FIGURE 10-17**
Worldwide epidemiology of analgesic nephropathy. The frequency of analgesic nephropathy in patients with end-stage renal diseases (ESRD) varies greatly within and among countries [14–16]. The highest prevalence rates of end-stage renal disease from analgesic nephropathy occur in South Africa (22%), Switzerland and Australia (20%), Belgium (18%), and Germany (15%). In Belgium, the prevalence is 36% in the north and 10% in the south. In Great Britain, the rate is 1% nationwide; in Scotland it is 26%. In United States, the rate is 5% nationwide, 13% in North Carolina, and 3% in Washington, DC. In Canada, the rate is 6% nationwide.

**FIGURE 10-18**
Prevalence of analgesic nephropathy versus nephropathy with unknown cause. Cross-national comparisons in Europe indicate that the proportion of cases of end-stage renal disease attributed to analgesics varies considerably; however, it is inversely proportional to unknown causes. These findings suggest an underestimation of the prevalence of analgesic nephropathy in several countries, probably owing to the lack of well-defined criteria for diagnosis [13,15]. EDTA—European Dialysis and Transplant Association. (From Elseviers and coworkers [13]; with permission.)
10.8 Tubulointerstitial Disease

A. The risk factor for end-stage renal disease of unknown cause is increased in relationship to the cumulative intake of acetaminophen as well as nonsteroidal anti-inflammatory drugs but not to aspirin. Moreover, mixtures containing several analgesic compounds were shown to be more nephrotoxic than are simple drugs.

B. In Belgium, the prevalence of analgesic nephropathy in 1991 was strongly correlated with sales of analgesic mixtures in 1983. Rs—coefficient of correlation. (A, Adapted from Perneger and coworkers [17]; B, adapted from Elseviers and De Broe [18]; with permission).

C. Example of papillary calcifications on CT scan. (Adapted from Elseviers and De Broe [19]; with permission).

D. PERCENTAGES OF SENSITIVITY AND SPECIFICITY

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in renal size</td>
<td>95</td>
<td>10</td>
</tr>
<tr>
<td>Bumpy contours</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>Papillary calcifications</td>
<td>87</td>
<td>97</td>
</tr>
</tbody>
</table>

FIGURE 10-19
Risk of analgesic nephropathy associated with specific types of analgesics. The initial reports of analgesic nephropathy chiefly concerned phenacetin mixtures. Phenacetin has been replaced with acetaminophen in analgesia mixtures without significant changes in the cause of analgesic nephropathy in some countries [15].

FIGURE 10-20
High performance of computed tomography (CT) scan for diagnosing analgesic nephropathy. Three criteria may be used to diagnose analgesic nephropathy by CT scan: decrease in renal size, measured by the sum of both sides of the rectangle enclosing the kidney at the level of the renal vessels (A); indentations counted at the level at which most indentations are present (more than three are qualified of bumpy contours) (B); and papillary calcifications (C). Percentages of sensitivity and specificity are given for the three criteria (D). (Adapted from Elseviers and De Broe [19]; with permission).
Toxic Nephropathies

Malignancies of the urinary tract and their association with analgesic nephropathy. Malignancies of the renal pelvis and ureters were reported in up to 9% of patients with analgesic nephropathy. This high prevalence can be explained by the appearance of carcinogenic substances in the major pathways of the metabolism of phenacetin. Probable carcinogenic substances are indicated by a plus sign.

Malignant uroepithelial tumors of the upper urinary tract in patients with analgesic nephropathy. A, Pyelogram showing a filling defect, indicating a tumor of the renal pelvis. B, Retrograde pyelography showing a long malignant stricture of the ureter, causing ureteral dilation and hydronephrosis. (Courtesy of W Lornoy, M D, OL Vrouwziekenhuis, M D.)
**Exposure to Cyclosporine**

**FIGURE 10-23**
Toxicity of cyclosporine. Cyclosporine is a neutral fungal hydrophobic 11-amino acid cyclic polypeptide. Cyclosporine is metabolized by hepatic cytochrome P450 to multiple less active and less toxic metabolites. Drugs that inhibit cytochrome P450 enzymes such as ketoconazole, verapamil, diltiazem, and erythromycin increase the concentration of cyclosporine and may thus precipitate renal side effects [20,21].

**FIGURE 10-24**
Cyclosporine and hypertension. Hypertension can develop in 10% to 80% of patients treated with cyclosporine, depending on dosage and length of the exposure. Cyclosporine increases cytosol calcium and, thus, enhances arteriolar smooth muscle responsiveness to vasoconstrictive stimuli. Vasoconstrictive effects of cyclosporine also are mediated by enhanced thromboxane action, sympathetic nerve stimulation, and release of endothelin. Renal vasoconstriction results in salt retention and hypertension. In chronic exposure to cyclosporine, hypertension also is a part of cyclosporine-induced chronic renal failure [22].

**FIGURE 10-25**
Pathogenesis of cyclosporine nephropathy. Chronic administration of cyclosporine may induce sustained renal vasoconstriction. Impairment of renal blood flow leads to tubulointerstitial fibrosis. Cyclosporine increases the recruitment of renin-containing cells along the afferent arteriole. Hyperplasia of the juxtaglomerular apparatus increases angiotensin II levels that, in turn, stimulate tumor growth factor-ß (TGF-ß) secretion, resulting in interstitial fibrosis [20].
FIGURE 10-26
Cyclosporine (CyA) nephrotoxicity in nonrenal diseases. A, Patients treated with cyclosporine (7.5 mg/kg) for psoriasis experienced a median decrease to 84% of the initial values in the glomerular filtration rate after 8 weeks of therapy. B, Of patients treated with cyclosporine (9.3 mg/kg) for autoimmune diseases, 21% showed cyclosporine nephropathy on biopsy, with a decrease to 60% of the initial values in renal function. C, Patients with cardiac transplantation treated with high doses of cyclosporine (10 to 6 mg/kg) developed a reduction to 57% of the initial values in renal function 36 months after transplantation. Patients treated with azathioprine did not show any reduction in renal function. D, Patients receiving cyclosporine (5 mg/kg) for uveitis for 2 years showed a decrease in glomerular filtration rate to 65% of the initial values. (Panel A adapted from Ellis and coworkers [23]; panel B adapted from Feutren and Mihatsch [24]; panel C adapted from Myers and Newton [25]; and panel D adapted from Deray and coworkers [26].)

FIGURE 10-27
Morphology of cyclosporine nephropathy on renal biopsy of a patient with cardiac transplantation. Two different types of lesions are seen in cyclosporine nephropathy. A, Arteriopathy: Hyalin, paucicellular thickening of the intima with focal wall necrosis results in narrowing of the vascular lumen (magnification × 300 periodic acid–Schiff reaction). B, A striped form of interstitial fibrosis characterized by irregularly distributed areas of stripes of interstitial fibrosis and tubular atrophy in the renal cortex. Tubules in other areas were normal (magnification × 100 periodic acid–Schiff reaction).
Exposure to Aminosalicylic Acid

Aminosalicylic acid and chronic tubulointerstitial nephritis. A. A 36-year-old man suffering from Crohn’s disease exhibited severe renal failure after 23 months of treatment with 5-aminosalicylic acid (5-ASA, or Pentasa, Hoechst Marion Roussel, Kansas City, MO). B. The first renal biopsy showing widening and massive cellular infiltration of the interstitium, tubular atrophy, and relative spacing of glomeruli. C. The second renal biopsy 8 months, after discontinuation of the drug and moderate improvement of the renal function, again showing important cellular infiltration of the interstitium tubular atrophy, and fibrosis. Several atrophic tubules are surrounded by one or more layers of α-smooth muscle actin positive cells. The patient had normal renal function on beginning treatment with 5-ASA. After 5 years of 5-ASA therapy, the patient demonstrated severe impaired renal function. The association between the use of 5-ASA and development of chronic tubulointerstitial nephritis in patients with inflammatory bowel disease (IBD) has gained recognition in recent years [27,28]. (Courtesy of M E De Broe, M D.)
Ochratoxin nephropathy. Ochratoxin A is a mycotoxin produced by various species of Aspergillus and Penicillium. Ochratoxins contaminate foods (mainly cereals) for humans as well as for cattle. Ochratoxins are mutagenic, oncogenic, and nephrotoxic. Ochratoxins are responsible for chronic nephropathy in pigs and also may be the cause of endemic Balkan nephropathy and some chronic interstitial nephropathies seen in North Africa and France [29].

**Clinical Features of Balkan Nephropathy**

- Residence in an endemic area
- Occupational history of farming
- Progressive renal failure
- Microproteinuria of tubular type
- Unremarkable urinary sediment
- Small and shrunken kidneys
- Associated urothelial tumors

Clinical features in Balkan nephropathy. Balkan nephropathy is characterized by progressive renal failure in residents (generally farmers) living in endemic areas for over 10 years. The urinary sediment is unremarkable and no proteinuria is seen, except for a microproteinuria of tubular type. The kidneys are small and shrunken. Urothelial cancers are frequently associated with Balkan nephropathy [29,30].

Endemic Balkan nephropathy. Endemic nephropathy is encountered in some well-defined areas of the Balkans. Distribution (dark areas) is along the affluents of the Danube, in a few areas on the plains and low hills owing to high humidity and rainfall. (From Stefanovic and Polenakovic [30]; with permission.)
FIGURE 10-32
Pathology of Balkan nephropathy. Balkan nephropathy is characterized by pure interstitial fibrosis with marked tubular atrophy (A) and by hyperplasia of the myocythial cells with narrowing of the lumen of the vessel (B) (From Stefanovic and M. Polenakovic [30]; with permission).

FIGURE 10-33
Pathology of ochratoxin nephropathy. In addition to interstitial fibrosis, large hyperchromatic nuclei in tubular epithelial cells are shown by the arrow (interstitial caryomegalic nephropathy). (Masson trichrome stain, magnification x 160.) The renal biopsy was obtained from a woman from France who had renal failure (creatinine clearance 40 mL/min) without significant proteinuria and urinary sediment abnormalities. Ochratoxin levels were 367 and 1810 ng/mL, respectively, in the patient’s blood and urine. (From Godin and coworkers [29].)

FIGURE 10-34
Balkan nephropathy and ochratoxin A in food. A survey of home-produced foodstuffs in the Balkans has revealed that contamination with ochratoxin A is more frequent in areas in which endemic nephropathy is prevalent (endemic areas) than in areas in which nephropathy is absent. (Adapted from Krogh and coworkers [31].)

FIGURE 10-35
Balkan nephropathy and urothelial cancers. Urothelial cancers appear as a frequent complication of Balkan nephropathy. An increased prevalence of upper tract urothelial tumors is described in inhabitants of areas in which Balkan nephropathy is endemic. (Adapted from Godin and coworkers [29].)
Exposure to Chinese Herbs

A. CHINESE HERBAL MEDICINE

<table>
<thead>
<tr>
<th>Chinese Name</th>
<th>Western Name</th>
<th>Chemical Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han fang-ji</td>
<td>Stephania tetrandra</td>
<td>Tetrandrine</td>
</tr>
<tr>
<td>Guang fang-jí</td>
<td>Aristochia fang chi</td>
<td>Aristochia acid</td>
</tr>
</tbody>
</table>

FIGURE 10-36

Epidemiology of Chinese herb nephropathy. Chinese herb nephropathy was described for the first time in Belgium in 1993 [32]. A peak incidence of new cases of women with rapidly progressive interstitial nephritis in Brussels during 1992 lead to suspicion of a new cause of renal disease. The relationship between this new renal disease and the recent introduction of Chinese herbs (namely, Stephania tetrandra) in a slimming regimen was established [32]. The withdrawal from the market of this herb has decreased the incidence of interstitial nephritis in Brussels, Belgium.

FIGURE 10-37

Role of Aristochia in Chinese herb nephropathy. Stephania tetrandra was the Chinese herb chronologically associated with the development of Chinese herb nephropathy. However, tetrandrine, the alkaloid characterizing Stephania tetrandra was not found in the capsules taken by the patients. In fact, confusion between Stephania tetrandra and Aristochia fang chi was done in the delivery of Chinese herbs in Belgium [33]. Chinese characters and the pingin name of Stephania tetrandra (Han fang-ji) are identical to that of Aristochia fang chi (Guang fang-jí). Investigations conducted on batches of Stephania tetrandra powders distributed in Belgium have shown that most of them contained aristochic acids (characteristic of Aristochia) and not tetrandrine (From Vanhaelen and coworkers [33] and P Daenens, Katholiek Universiteit Leuven, Belgium, report of expertise 1996.)
**DNA ADDUCTS FORMED BY ARISTOLOCHIC ACID IN RENAL TISSUE**

<table>
<thead>
<tr>
<th>Chinese Herb Nephropathy (n = 5)</th>
<th>Controls (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7–5.3 per 10^7 nucleotides</td>
<td>0</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES OF CHINESE HERB NEPHROPATHY**

- Rapidly progressive renal failure
- Microproteinuria of tubular type
- Unremarkable urinary sediment
- Small and shrunken kidneys
- Valvular heart diseases (dexfenfluramine-associated therapy), 30%
- Associated urothelial cancers

**FIGURE 10-39**
The clinical features of Chinese herbs nephropathy are characterized by rapidly progressive renal failure without both urinary sediment abnormalities and proteinuria except for a microproteinuria of tubular type. The kidneys are small and shrunken. Vascular heart diseases are associated in 30% of cases (probably owing to dexfenfluramine administered with the Chinese herbs for slimming purposes) [35]. Some cases of associated urothelial cancers also are described [36,37].

**FIGURE 10-38**
DNA aristolochic acid adducts in kidney tissues of patients with Chinese herbs nephropathy. The role of Aristolochia in the pathogenesis of Chinese herbs nephropathy was confirmed by the demonstration of DNA aristolochic acid adducts (a biomarker of aristolochic acids exposure) in renal tissue of patients with Chinese herbs nephropathy, whereas these adducts were absent in the renal tissue of control cases. (Adapted from Schmeiser and coworkers [34].)

**TABLE 10-16**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chinese Herb Nephropathy (n = 5)</th>
<th>Controls (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria of tubular type</td>
<td>0.7–5.3 per 10^7 nucleotides</td>
<td>0</td>
</tr>
</tbody>
</table>

**FIGURE 10-40**
Photographic image of the pathology of Chinese herbs nephropathy. Chinese herbs nephropathy is characterized by a large reduction in kidney volume. Moreover, an associated tumor of the lower ureter is shown.

**FIGURE 10-41** (see Color Plate)
Pathology of Chinese herb nephropathy. The major pathologic lesion consists of extensive interstitial fibrosis with atrophy and loss of the tubules, predominantly located in superficial cortex [38,39]. A, A low-power view of transition between superficial cortex (left) and deep cortex (right) shows an extensive interstitial fibrosis with relative sparing of glomeruli. (Masson trichrome stain, magnification × 50.) B, A normal glomerulus surrounded by a paucicellular interstitial fibrosis and atrophic tubules. (Masson's trichrome stain, magnification × 300.)
Microproteinuria and neutral endopeptidase enzymuria in Chinese herbs nephropathy. Proximal tubular injury in Chinese herbs nephropathy is demonstrated by a significant increase in urinary excretion of microproteins (Clara cell protein, CC16; β2-microglobulin [β2-m] and retinol binding protein [RBP]) as well as a decrease in urinary excretion of neutral endopeptidase (NEP) a marker of the brush border tubular mass. (Adapted from Nortier and coworkers [40].)

Chinese herbs nephropathy and renal pelvic carcinoma. Urothelial cancers are associated with Chinese herbs nephropathy [36,37]. Shown is a filling defect (arrow) in the renal pelvis in an antegrade pyelogram obtained from a patient with Chinese herbs nephropathy and hematuria. (From Vanherweghem and coworkers [37]; with permission.)
FIGURE 10-44
Pathology of urothelial tumors associated with Chinese herbs nephropathy. Microscopic pattern is shown of a lower urothelial tumor obtained by ureteronephrectomy of a native kidney in a patient with transplantation who has Chinese herbs nephropathy (the macroscopic appearance of the nephrectomy is shown in Fig. 10-40). A, Part of the urothelial proliferation. Plurifocal thickening of the urothelium is present. (Hematoxylin and eosin stain x 50.) B, In situ transitional cell carcinoma with high mitotic rate. (Magnification x 400 periodic acid-Schiff reaction.)

FIGURE 10-45
Effects of steroids on the evolution of renal failure in Chinese herbs nephropathy. Steroid therapy was shown to decrease the evolution of renal failure in a subgroup of patients with Chinese herbs nephropathy [41]. The evolution is shown of the 1/P creatinine ratio of patients with Chinese herbs nephropathy, 12 of whom were treated with steroids as compared with 23 not treated with steroids (control group). In the control group the 1/P creatinine curve was limited to 6 months of follow-up because at 12 months, 17 of the 23 patients were on renal replacement therapy. (From Vanherweghem and coworkers [41]; with permission.)

FIGURE 10-46
Of interest is the association between chronic renal interstitial fibrosis and urothelial cancers. This association appears, at least, in three chronic toxic nephropathies: analgesic nephropathy, Balkan nephropathy, and Chinese herbs nephropathy. This association indicates that nephrotoxins promoting interstitial fibrosis (analgesics, ochratoxins, and aristolochic acids) also may be oncogenic substances.

TOXIC CHRONIC INTERSTITIAL NEPHROPATHIES WITH UROTHELIAL CANCERS
- Analgesic nephropathy (phenetidin compounds)
- Balkan nephropathy (ochratoxins)
- Chinese herbs nephropathy (aristolochic acids)
References