Avian Kidney Disease

Part I: Types of Renal Disease

M. Scott Echols, DVM, Diplomate ABVP - Avian Practice

Director of Avian Medical and Surgical Services, Westgate Pet and Bird Hospital, 4534 Westgate Blvd, Suite 100, Austin, Texas 78745, USA.

The information contained within Parts 1-3 was taken from: Echols MS (2006). Evaluating and treating the kidneys. In: Harrison GH and Lightfoot TL (eds). *Clinical Avian Medicine Vol II*, Spix Publishing, Palm Beach, Fl. pp 451-491, with permission from Spix Publishing, Inc. References were not listed due to the scope and number and the reader is asked to contact the author or review the above listed book for specific reference citations and sources.

Avian renal disease comes in many forms and may be associated with multiple diseases and etiologies. Understanding the potential causes of renal disease in birds helps with both diagnosis and treatment. This in-depth discussion will cover potential mechanisms, consequences, etiologies and specific reported forms of avian renal disease.

General Mechanisms and Consequences of Renal Injury

Initiation of renal disease

Proposed mechanisms of the process of initiation of renal injury and perpetuation of disease are complex, but have been described in mammals. These 'mammalian' mechanisms may or may not apply directly to birds, but help form the basis on which some treatments are considered. For this reason, some of the inflammatory cascade that occurs with renal disease is described.

The products resulting from the arachidonic acid cascade have effects throughout the body. For the purposes of this discussion, the cyclo-oxygenase pathway of the arachidonic acid cascade will be briefly covered.

In studied species, the renal medulla and papilla are a rich source of the group of enzymes collectively called prostaglandin synthetases. The action of, the prostaglandin synthetase, cyclo-oxygenase upon arachidonic acid results in the formation of numerous prostaglandins (PE_2, $PGF_{2\alpha}$, and PGD_2) and thromboxanes (thromboxane A_2 [TXA] and thromboxane B_2) all of which have varying actions on cells. In response to renal ischaemia and vasoconstriction, prostaglandin and thromboxane production is altered (primarily increased). These 'alterations' subsequently result in varying effects on the body and kidney including changes in renal vascular resistance, blood flow, recruitment of inflammatory cells and other physiologic effects. Non-steroidal anti-inflammatories act to inhibit prostaglandin synthetase and represent another method by which to 'alter' these arachidonic acid by-products and their subsequent actions.

Specifically, TXA production, secondary to toxic or ischemic injury, is considered the main cause of renal vasoconstriction associated with acute renal failure and is believed to play a pathogenic role in

many forms of kidney disease. Thromboxane A_2, again an eicosanoid derived from the action of cyclooxygenase on arachidonic acid, is produced by many mammalian cells including glomerular epithelial and mesangial cells, renal medulla tubular cells and especially platelets.

In mammals, TXA causes mesangial cell contraction and is a potent vasoconstrictor. Both of these actions can result in decreased glomerular filtration rate (GFR). Renal vasoconstriction decreases GFR and delivery of oxygen and nutrients to tubular cells, resulting in renal damage. Thromboxane A_2 also promotes platelet aggregation and may be partially responsible for hemostatic abnormalities noted with renal disease. As histologic progression of renal disease continues when TXA is inhibited, it is possible that TXA only helps initiate kidney pathology.

The above-described outcomes of increased TXA production only serve to show some of the possible negative effects of one by-product created as a result of renal injury. Managing these negative effects may be needed, especially when a clearly identified cause, such as bacteria in the kidney parenchyma, is not found. This then brings up the reasoning behind using products such as omega-3 fatty acids and low-dose NSAIDS when managing some forms of renal disease.

Brief review of selected potential consequences of renal disease

Kidneys are dynamic organs and are directly or indirectly associated with multiple body systems. As a result, renal disorders can lead to, or be caused from, multiple other disease processes. Some processes such as hypertension, hypercoagulability and the nephrotic syndrome are well described in mammalian renal disease but are never, or rarely, discussed in the avian literature.

Hemostatic abnormalities:
Abnormalities of hemostasis are noted with some forms of renal disease and may lead to additional kidney or systemic disease. Platelet aggregation and activation occur secondary to complement activated antigen-antibody interactions and renal endothelial damage. Activated platelets may then release vasoactive and inflammatory products (including TXA), growth stimulation factors and facilitate the coagulation cascade. These reactions can result in glomerular damage via glomerular basement membrane thickening and potentially, hyalinization and sclerosis.

Fibrinous renal vessel thrombi have been noted in red-faced lovebirds (*Agapornis pullarius*) with membranous glomerulopathy and in chickens with *Erysipelothrix rhusiopathiae* sepsis. However, thrombus formation has been suggested to be rare in birds compared with mammals. Using multiple staining methods, Phalen could not confirm that 'fibrin-like' thrombi noted histologically in various psittacine birds with polyomavirus-associated glomerulopathy were truly composed of fibrin.

Gastrointestinal complications:
Gastrointestinal ulcerations are reported in some animals with uraemia and advanced renal disease but are rarely mentioned concurrently in clinical reports of birds with kidney disorders. In chickens, gizzard erosions have been associated with naturally-occurring urolithiasis. Due to the overall lack of reports in the reviewed literature, it is unlikely that birds with renal disease develop gastrointestinal ulcers.

Intestinal inflammation may lead to renal disease. In humans, inflammatory bowel disease (IBD) can be related to renal disorders. In humans, those with IBD have a 10-100 times greater risk of developing nephrolithiasis compared with other hospitalized patients. Human IBD patients may also have an increased risk of glomerulonephritis and tubulointerstitial nephritis. The avian coccygeomesenteric vein drains the mesentery of the hindgut into the hepatic portal and/or the renal portal vein. Colitis may serve as a source of infectious agents, toxins and inflammatory products to

the avian kidney if blood flow draining the colon is diverted into the renal vasculature. As a result, antibiotic therapy should be considered in all cases of colitis, especially when renal disease is suspected or confirmed.

Abnormal lipid metabolism:
Aberrant lipid metabolism as evidenced by increased serum total cholesterol, low density lipoproteins and triglycerides has been noted in humans, cats and dogs with renal disease. In rats, lipid accumulation is known to stimulate glomerular mesangial cell and excess matrix production known as glomerulosclerosis. Hyperlipidaemia has been associated with glomerulosclerosis and/or loss of renal function in rats, guinea pigs, rabbits and dogs. Glomerulosclerosis is histologically similar to artherosclerosis and may share a common pathogenesis. Although scarcely noted in the avian literature, abnormal lipid intake, production and/or metabolism may be associated with renal disease in birds, as described below.

High cholesterol diets may actually induce renal disease in birds. Pigeons supplemented with dietary cholesterol (0.2%, 0.4% and 0.5% of the diet) had a high incidence of end-stage renal disease, atherosclerosis and increased mortality rate compared with controls. Although specific data was not presented, pigeon mortality was 'influenced largely by the degree and duration of hypercholesterolaemia'. The implication herein is that diets high in cholesterol may lead to renal disease, at least in pigeons.

Gout
Renal disease may lead to numerous other conditions, including gout, which can further damage the kidneys or additional body systems. Gout reportedly may be caused by reduced excretion of urates or by increased dietary protein (although this has been disputed, see 'Treatment and Management of Avian Renal Disease'). Dehydration and many forms of renal disease including obstructed ureters and general kidney damage can result in decreased uric acid elimination. As blood levels of uric acid rise and exceed the solubility of sodium urate in plasma (hyperuricaemia), monosodium urate crystal precipitation is initiated. Roudybush concluded that 'gout may not prove to be a nutritional disease in birds except under unusual circumstances such as deficiency of vitamin A'.

Visceral gout results secondarily from elevated plasma uric acid levels and its resultant deposition on visceral organs. During visceral gout, urate depositions are commonly found on the pericardium, liver and spleen. Additionally, uric acid deposits are noted histologically within the lamina propria of the proventriculus, ventriculus and sometimes intestine and within the kidney, but can be found on or in any tissue. Visceral gout may appear as a white coating when on the capsular surface of affected tissue. Visceral gout has been associated with multiple forms of renal pathology. Experimentally, visceral gout has been induced in chickens fed excessive dietary calcium and a diet deficient in vitamin A, administered various nephrotoxic agents and following ureteral ligation and urolithiasis.

Articular gout results from the accumulation of urates in the synovial capsules and tendon sheaths of the joints. Diffuse urate deposits on visceral surfaces do not occur in articular gout. However, visceral and articular gout can be present in the same bird. Gross lesions typically consist of soft swellings on the feet at the metatarsophalangeal and interphalangeal joints. These swellings appear to be painful as noted in clinical cases. Spontaneous articular gout in birds without underlying renal pathology is relatively uncommon and appears to have a hereditary basis, at least in chickens.

Continuing damage
Once renal damage occurs, persistent and progressive kidney damage is likely to occur, even if the initial insult is treated and 'cured'. In humans, 50-60% of children with pyelonephritis develop irreversible lesions of the renal parenchyma. Although no refereed literature describes the post-

treatment progression of renal lesions in living avian patients, the author reported repeated kidney biopsies in numerous birds in effort to help evaluate their clinical progression. Repeat biopsies have shown, that in birds with histologic confirmation of various kidney diseases, some mild renal lesions persist even if the patient is clinically normal or improved. When repeating kidney biopsies, the author has noticed no increase in scarring (gross or histologic lesions) or other abnormalities at the prior surgery sites, suggesting some treated birds have good regenerative and/or healing properties. Although these repeat biopsies are encouraging, the long-term health of these patient's kidneys is still unknown.

General Renal Disease Categories

Nephritis

Nephritis is simply inflammation of the kidney and may involve the interstitium, tubules and/or the glomerulus (although 'glomerulonephritis' is typically reserved for glomerular lesions). While 'pyelonephritis' has been described in birds this term is technically incorrect as avian species lack a renal pelvis. Nephritis is a non-specific description, but some histological patterns and (especially) identification of infectious organisms help define the aetiology.

Glomerulopathies

In the literature, glomerular disease has been loosely termed 'glomerulonephritis' but unless inflammation is specifically present, the term 'glomerulopathy' would be more appropriate. Glomerulonephritis describes inflammation of the glomerulus, usually considered mediated by the deposition of immune complexes or anti-glomerular basement membrane antibodies. A more accurate description of glomerular lesions, based on light and electron microscopy and immunohistochemistry, helps define the actual type of glomerulopathy present.

Glomerular disease is the most important cause of end-stage renal disease in humans worldwide and of chronic renal insufficiency/failure in dogs. Proteinuria is the hallmark sign of glomerulonephritis in mammals prior to the onset of clinical renal insufficiency. However, chicken leukocytes lack proteolytic enzymes that would potentially damage the glomerular basement membrane (and allow protein leakage) and birds may in fact, not develop pathologic proteinuria with glomerulopathies. In one study, no pathologic proteinuria was found in chickens with experiemental autoimmune glomerulonephritis. As noted below, glomerulopathies are well documented in avian species but numerous differences exist when comparing this disease in birds and mammals.

The cause of glomerulopathies is generally assumed to be immune-mediated, but the inciting aetiology is often unknown. Membranous nephropathy, the most common cause of nephrotic syndrome in humans, is usually idiopathic and specific etiologies are identified in only 20% of cases. With few exceptions, the causes of glomerulopathies in birds are poorly studied. Polyomavirus infection is associated with membranous glomerulopathy in psittacines. Glomerular pathology has been noted in chickens with various septic conditions and naturally occurring multicentric histiocytosis. Glomerulopathies can also be induced experimentally in chickens by intravenous fungal injections, *Plasmodium gallinaceum* infections and by feeding aflatoxin. Grossly normal 6 to 7 week old broiler chickens at slaughter have been diagnosed with proliferative glomerulonephritis of unknown aetiology. Proliferative glomerulopathy can be induced in pigeons fed diets high in cholesterol. Siller has suggested that because of the extensive (dual) renal blood supply, severe chronic glomerulonephritis may persist without any clinical manifestation in birds. Siller further suggests that avian glomerulonephritis may be present in far more birds than it is currently diagnosed.

Although humorally mediated immunity is frequently discussed as the aetiology of glomerulopathies, research has strongly suggested that cell mediated immunity plays an important role in producing

glomerular disease in chickens and other animals. Under experimental conditions, cyclophosphamide bursectomized (humorally deficient) chickens develop glomerulonephritis. Although gross histologic lesions are similar, bursectomized chickens develop no IgG glomerular basement membrane deposits compared to controls when glomerulonehpritis is induced in both groups. These and other findings, support the conclusion that cell mediated immunity, or some other non-humoral immune response, is responsible for inducing glomerulonephritis in chickens. Interestingly, birds with even massive mesangial enlargement, in the above-described study, maintained normal glomerular filtration. Due to the small centrally oriented avian glomerular mesangium, the capillary loops were only slightly displaced to the periphery without compromising function. Given our current knowledge regarding the differences between avian and mammalian species, renal biopsy is the best way to definitively diagnose glomerular (and other) kidney diseases in birds. (See 'Diagnosis of Avian Renal Disease')

Infectious diseases

Bacterial:

Certain patterns may be expected with bacterial nephritis. Chickens experimentally infected with *E. coli* [E. coli $0_1K_{67}(B_{12})$], *Staphylococcus aureus* and *Actinomyces pyogenes*, developed a fairly consistent pattern and progression of renal disease. Birds inoculated subcutaneously developed more severe renal lesions and these lesions were noted earlier than those exposed to bacteria per os. Additionally, lesions were more severe in birds infected with *E. coli* and *S. aureus* compared to the slight reaction induced from *A. pyogenes*. Gross renal changes included congestion, enlargement and hemorrhagic foci. Although specific timelines were not given in regards to lesion development, bird kidneys were histologically examined at 4, 7, 10, 14 and 21 days post-inoculation. The 'early stage' lesions consisted of acute interstitial nephritis (mainly lymphocytes, plasma cells and macrophages), prominent congestion and hemorrhage. The lesions progressed to nephrotoxic nephritis and included tubular epithelial cell degeneration and necrosis with the formation of hyaline casts and eosinophilic material. 'Later' histology showed decreased congestion, persistence of mononuclear cells, introduction of connective tissue running around hyperplastic tubules and glomerular lesions.

Certain renal histologic characteristics, with or without organisms present, may suggest an ascending or haematogenous bacterial infection in the avian kidney. The typical lesions suggestive of bacterial nephritis include tubular dilatation and impaction with inflammatory cells. As nephritis becomes chronic, tubular necrosis, cyst formation, distortion and interstitial fibrosis with mononuclear cell infiltration become evident.

Using sterile collection and culture methods, bacterial nephritis is definitively diagnosed by recovering bacterial organisms from affected kidneys. Light microscopic identification of bacteria within renal tissue may be difficult as has been noted in dogs and swine with renal disease. In a Coturnix quail processing plant outbreak, *Erysipelothrix rhusiopathiae* was cultured from multiple organs. While the kidneys were swollen and congested, no organisms were specifically noted histologically which emphasizes the importance of tissue culture. Specifically, *Escherichia coli* has been identified in chickens as a cause of bacterial nephritis ('pyelonephritis'). As a component of systemic paratyphus, *Salmonella typhimurium* var. Copenhagen was identified in kidney tissue and most frequently caused interstitial nephritis in a study of 78 experimentally infected pigeons. The same organism was also recovered from kidney tissue, as a component of systemic salmonellosis, in pigeons from a large production colony. As is likely true of most viral and fungal renal diseases, bacterial nephritis is often a component of systemic infection and multiple organs may be involved. In summary, any septicaemia can potentially result in kidney infection and inflammation.

Viral:
Viruses perhaps have the most varied effect on avian kidneys. Numerous viruses may infect and affect avian kidneys. Histologic patterns are highly variable as some viruses directly affect the kidneys, such as pheasant coronavirus-associated nephritis, while others like psittacine herpesvirus and polyomavirus damage renal tissue as a part of a more systemic process.

Other viruses may cause minimal (or little) to no renal disease but can be identified in the avian kidney because of viraemia and or viral replication and transmission through the urinary tract. For example the reovirus that causes viral arthritis of chickens infects the kidneys within a few days of inoculation, but causes minimal, if any, renal lesions. Some viral infections, such as the West Nile virus, are best identified in the kidney and provide an additional reason to save extra renal tissue (frozen and/or formalinized) for later testing.

Parasitic:
Renal coccidia
Primary and secondary renal parasites have been noted throughout the avian literature and some contribute to significant morbidity and mortality. Renal coccidiosis, found predominately in some waterfowl and marine species, is the most frequently reported avian renal parasite in those species and has been clearly associated with disease in some cases. Reports of various other parasitic diseases affecting the kidneys are noted, but their significance is not well established.

Several renal coccidia species have been identified and primarily include *Eimeria truncata*, *E. somateriae*, *E. christianseni*, *E. boschadis*, *E. gaviae*, *E. fraterculae*, *E. goelandi* and *E. wobeseri*. Disease has ranged from mild histologic changes found incidentally (most species) to acute renal failure and death such as in juvenile eiders (*Somateriae mollissima*) and domestic geese (*Anser anser domestica*). Flock mortality in domestic geese due to *E. truncata* has been reported to be as high as 87%.

Renal *Eimeria* sp. oocysts are passed in feces via the ureter and sporulate rapidly in the environment. Affected birds typically breed in large colonies or are otherwise under crowded conditions, which likely favors transmission of this parasite. The prepatent period appears to range between species and has included 5 to 21 days. Although transmission between different avian species is not clear, one study suggested that renal coccidia of geese do not infect ducks.

The clinical, gross and histologic abnormalities noted with renal coccidiosis seem to be fairly consistent across affected species. Most clinically affected species are young birds. Clinically affected birds are typically emaciated and may have diarrhea with or without blood. It should be kept in mind that many reported birds are wild and have also had intestinal parasites that may contribute to the described clinical signs. Grossly, the kidneys are often enlarged with white to yellowish nodules containing urates and/or oocysts.

Cytologic smears of renal tissue and ureters often contain different endogenous stages of coccidian.oocysts. The renal tubules are parasitized and histologic lesions vary from mild dilatation to severe tubular destruction with associated degrees of inflammatory cell infiltrate (unusually mononuclear). The tubules are often distended with endogenous developmental stages (micro- and macrogamonts, macrogametes) and maturing *Eimeria* sp. oocysts. In severe cases, tubular nephrosis, necrosis and interstitial nephritis potentially causing significant renal dysfunction may be noted.

Sarcocystis

Numerous other parasites have been noted in the kidneys of birds, but oftentimes association with disease is not clear. Canaries *(Serinus canaries*) experimentally infected with *Sarcocystis falcatula* developed mild multifocal interstitial renal infiltrates and glomerular hypertrophy with mesangial hyperplasia that 'modestly progressed with duration of infection'. While precystic merogeny was primarily noted in the pulmonary tissue, infected canaries had low levels of merogeny in the kidney and other tissues. Similarly infected pigeons developed no renal lesions. Sarcocystis organisms have also been noted histologically in the renal parenchyma of cockatiels, but again the significance is unclear.

Microsporidia

Microsporidia (*Encephalitozoon* sp.) have been reported in numerous avian species with variable effects on the kidney. A psittacine beak and feather virus positive eclectus parrot (*Eclectus roratus*) had heavily parasitized (*Encephalitozoon hellem*) kidney cells with associated renal tubular distention. As has been noted in other reported cases, renal cellular reaction was minimal in the Eclectus. Similar histological lesions and parasite morphology and locations (liver, kidney and intestines) have also been reported in 3 species of lovebirds, budgerigars (*Melopsittacus undulatus*) and a double-yellow headed Amazon parrot. The author has also seen renal microsporidiosis in a canary (*Serinus canaria*) that presented for acute illness and died shortly thereafter. Histology confirmed that numerous microsporidial organisms (not further defined) were present in the renal tubules and were associated with tubular necrosis. Other histologic lesions were minimal to mild placing renal failure as the likely cause of death. Although it is not clear what role the kidney plays in disease, some believe that *E. hellem* is an avian and human pathogen and may be primarily found in immunocompromised individuals.

Cryptosporidia

Urinary tract cryptosporidiosis has also been noted in multiple bird species with varying associated disease. Although renal cryptosporidiosis is infrequently reported, it has been directly associated with kidney lesions in a four-month-old black-throated finch (*Peophila cincta*), an eight-week-old Sonnarat's jungle fowl (Gallus sonneratii), 4 month old pullets and adult laying hens. Four day-old chickens co-infected with Marek's disease virus have also been studied. Clinical signs ranged from acute death (finch and jungle fowl) to thinning, depression, leg weakness and respiratory distress (4-month-old pullets and 4-day-old chicks) to slightly increased morbidity and mortality (adult chickens). Pulmonary cryptosporidiosis was also a common feature of the pullets.

Similarities were noted among gross and microscopic findings. The affected black-throated finch and Sonnarat's jungle fowl had pale and swollen kidneys and all birds had some degree of tubular epithelial tissue change with organism colonization. The finch, adult layers, pullets and chicks also had interstitial nephritis, while the jungle fowl had no inflammatory response. Although no organisms were specifically found in the kidneys, a diamond firetail finch (*Stagnoplura bella*) with proventricular cryptosporidiosis also had similar tubular lesions in addition to multifocal amyloidosis (kidney included), severe, chronic urate nephrosis and protein and cellular tubular casts.

Increased incidence of visceral gout, 1-2% higher than expected mortality and numerous stages of *Cryptosporidium sp.* organisms within the epithelial cells lining the renal collecting tubules and ureters (of histologically evaluated kidneys) was found in egg laying chickens from a production facility. Visceral gout was likely caused by the partial ureteral obstruction resulting from heavy diffuse lymphoplasmacytic infiltration in the wall of the ureter and

(parasitised) epithelial wall hyperplasia. Regarding the experimentally infected chicks, the authors concluded that *Cryptosporidum baileyi* can be highly pathogenic and induce mortality and urinary tract infections in chickens infected with Marek's disease virus (an immunosuppressive effect). Several authors have hypothesized that urinary tract *Cryptosporidium* infection originates in the cloaca and retrogrades into the kidneys via the ureters. Although relatively uncommon, urinary tract cryptosporidiosis and associated disease seem to primarily be a concern in chickens, especially those with concurrent immunosuppressive illness.

Flukes

Scattered reports of renal flukes are noted in the literature. Spindle shaped eggs, belonging to the blood fluke *Dendritobilharzia anatinarum*, were identified in kidney tissue pressed between glass slides in mallards (*Anas platyrhynchos*). The birds died from severe enteritis, associated with blood fluke eggs, but no renal histology was described. Other schistosome's eggs may occasionally cause granulomatous ureteritis in waterfowl. Parasites of the genus *Renicola* may also parasitize the renal tubules of several waterfowl species. The renicolid flukes appear to have an indirect life cycle and likely first infect mollusks and then mature in the renal tubules of susceptible species. Eucotylid renal flukes may reside in the dilated ducts of the renal medulla of pigeon and passerine kidneys. They seldom cause problems and their eggs may be found in the feces and confused with other fluke eggs. Clinical descriptions of affected animals are poorly described.

Miscellaneous Parasites

Other parasitic diseases may also be found incidentally in the kidneys of birds. Visceral larval migrans lesions consisting of a granulomatous reaction surrounding intact or degenerate *Baylisascaris procyonis* larvae in the renal (and other tissue) parenchyma of the house sparrow (*Passer domesticus*) were noted in one study. As most of the mixed species of birds had neural larval migrans only, the renal lesions seemed comparatively uncommon. Chickens and pigeons have been experimentally infected with *Toxoplasma gondii* oocysts and evaluated for disease. While infected chickens developed no clinical signs and minimal evidence of infectivity, pigeons showed rapidly progressive disease (diarrhea, trembling, incoordination, death) and toxoplasma organisms in the kidney and other tissues. The authors stressed the importance of the pigeon crop in shedding the organisms with no emphasis on the kidneys. It is probable that other parasites can affect the avian kidney and should be kept as an unlikely or rare differential diagnosis for renal disease.

Fungal:

Fungal nephritis is uncommonly reported in birds. One chicken with renal and pulmonary cryptosporidiosis had *Aspergillus* sp. lesions in the lungs, air sacs, thoracic walls and kidneys. In a separate study of 4 day-old chicks coinfected with *Cryptospordium baileyi* and Marek's disease virus, one bird had necrotic renal aspergillosis. Fungal nephritis, caused by *Aspergillus flavus-oryzae* group, was the only lesion seen in a moribund grey-headed albatross. While focal coagulative necrosis, fibrous tissue and pronounced cellular reaction consisting of macrophages and multinucleated giant cells surrounding occasional fungal hyphae were noted, the lesions spared most of the renal tissue and did not account for the bird's poor condition. Given the close association between the air sacs and kidneys, direct extension from the respiratory system (rather than primary renal invasion) is likely the cause of the necrotic fungal lesions in the kidneys.

Nephrosis:
Nephrosis is a non-specific histopathologic change characterized as 'any degenerative, non-inflammatory lesion of the kidney, from cloudy swelling to necrosis, whatever the cause'. This is a microscopic diagnosis that cannot be made with gross observation. Due to its role in elimination, the avian kidney is vulnerable to the effects of many chemical toxins. Inflammatory changes may develop, especially if the condition persists, and may confuse the diagnosis. Siller notes that tubular lesions may be reversible if the noxious substance is removed, provided the pathologic changes are not too advanced. Causes of avian nephrosis have included avian malaria and hemoglobinuria, adenovirus infections, *Clostridium welchii* enterotoxaemia, and lead, zinc, cadmium, calcium, aminoglycosides, phenoxy acid, sodium, ochratoxin A, ethylene glycol, 2,4-D, cadmium and 3-chloro-p-toluidine (avicide) toxicities. This list is incomplete and only serves to emphasize the diversity of potential avian nephrosis-inducing agents. Although many toxins have been shown to induce nephrosis and other kidney diseases, renal lesions caused by specific toxicities are difficult to prove outside of a controlled study.

Hypertonic solutions may also cause a specific osmotic nephrosis in 'birds'. Hypertonic sucrose solutions (concentration not recorded) given intravenously have caused extensive vacuolation of the proximal convoluted tubules in birds. Similar renal findings have been noted in other animals and man when injected with hypertonic sugar solutions and dextran intravenoulsy.

Selected toxic and nutritional diseases

Vitamin D intoxication:
Vitamin D intoxication has been discussed in birds. Vitamin D is converted in the liver to 25-hydroxycholecalciferol and then further hydroxylated to 1,25-dihydroxycholecalciferol in the kidney. Avian macrophages have the capacity to convert vitamin D to its active form 1,25-dihydroxycholecalciferol. It is 1,25-dihydroxycholecalciferol that enhances the intestinal absorption of calcium and phosphate.

As a result of excessive calcium uptake, visceral calcinosis, nephrocalcinosis, visceral gout and urate nephrosis are considered frequent complications of vitamin D intoxication in birds. Symptoms of hypervitaminosis D include hypercalcaemia, anorexia, nausea, polyuria, polydipsia, demineralization of bones, disorientation, painful joints and muscle weakness. In normal 'animals' experimentally subjected to hypervitaminosis D, 25-hydroxycholecalciferol, and not 1,25-dihydroxycholcalciferol, increase in the serum. Chicks fed *Cestrum dirunum* leaves, which contain an analog of 1,25-dihydroxycholecalciferol, develop nephrocalcinosis and hypercalcaemia but the ultrastructural lesions are different than is noted with vitamin D toxicity.

Hypervitaminosis D may occur when feeding developing birds vitamin D containing supplements. A 3.5 month-old blue and gold macaw (*Ara ararauna*) and 5.5 month-old salmon-crested cockatoo (*Cacatua moluccensis*) from the same household developed polyuria, polydipsia and anorexia after being fed a diet (including supplements) with excessive vitamins A and D_3 and of calcium. The cockatoo was hypercalcaemic and had radiographic evidence of renomegally. Hypercalcaemia, hyperphosphataemia, hyperuricaemia and elevated plasma creatine kinase were noted in the macaw. The calculated levels of vitamins A (119,000 IU/ kg feed) and D_3 (26,790 IU/ kg feed) were over 20 times the recommended levels (5000 IU/ kg feed and 1000 IU/ kg feed, respectively). Vitamin D_3 is considered toxic at 4 to 10 times the recommended amount. The cockatoo died 6 days after presentation and had chronic interstitial nephritis and calcifications in the kidney, proventriculus and lung. The macaw improved gradually and became disease free after discontinuing the supplemental

vitamins and minerals. Hypercalcaemia was attributed to oversupplementation with calcium and the vitamin mixture.

It has been suggested that African grey parrots (*Psittacus erithacus*) may be susceptible to hypervitaminosis D. Although, no reviewed papers support this statement. Any bird species can potentially be susceptible to hypervitaminosis D.

Hypercalcinosis:
High calcium intake has also been directly correlated with renal disease in birds. Broiler chicks fed 3.27% calcium in the diet for 15 weeks, starting at 18 days old, developed numerous renal lesions throughout the study. Nephrosis was noted by 7 weeks and progressed to nephritis (10 weeks), visceral gout (11 weeks) and replacement of the kidney parenchyma with urate granulomas (12 weeks). In two separate studies, some growing chickens fed 3% calcium and 0.38% and 0.4% phosphorous, respectively, developed renal lesions such as nephritis and ureteral and collecting duct occlusion due to probable calcium urate salts. Limestone sand substrate (13.48% calcium and 0.02% phosphorous) was associated with rickets and nephrocalcinosis in young ostriches. Clinically affected birds returned to normal and no new cases developed once the substrate was changed to acid-washed sand (0.03% calcium and 0.02% phosphorous).

In a study involving young and adult budgerigars (*Melopsittacus undulatus*), increasing dietary calcium levels were shown to be more renal toxic than was excess vitamin D_3. Parent birds were fed diets containing 0.3%, 0.7% and 1.5% dietary calcium with a range of 500, 1,000, 1,500 and 3,000 IU/kg/feed of vitamin D_3. The adults subsequently fed the young the same diet. When fed a diet containing 3,000 IU/kg/feed of vitamin D_3 there was a questionably increased mortality rate only in the birds receiving 1.5% dietary calcium. However, there was a clear correlation with mild and severe metastatic (renal) mineralization in birds fed 0.7% and 1.5% calcium, respectively. The young birds fed 0.7% and 1.5 % calcium died by 24-32 days old and never fledged (32-35 days). Growth rate and hatchability were poor only in the groups fed 1.5% calcium. While only a few adults died by 5 months on diets containing 1.5% calcium, most had metastatic renal mineralization when fed 0.7% calcium. Birds fed 0.3% calcium had no evidence of metastatic mineralization and had good hatchability and growth rates. This study suggests that some species, such as budgerigars, may be very sensitive to dietary calcium levels and that supplementation should be used cautiously.

Hypovitaminosis A:
Hypovitaminosis A may also lead to renal disease in avian patients. In birds with hypovitaminosis A, the ureters and renal collecting ducts may undergo metaplasia changing the normal double-layered epithelium to keratinized stratified squamous tissue. These epithelial changes can result in decreased mucin production and excessive keratin leading to plug formation and ureteral obstruction. The consequential (secondary) lesions include renal tubular dilitation and necrosis, tophus formation and interstitial fibrosis. Nephrosis, nephritis, visceral gout and severe replacement of the kidney parenchyma by urate granulomas were noted in broiler chicks fed vitamin A deficient diets for 15 weeks starting at 18 days old.

High cholesterol diets:
Cholesterol supplemented in the feed can induce significant renal disease in pigeons. Crystalline cholesterol and 10% lard were added to the diets of these pigeons under experimental conditions. The kidneys of some affected birds are firm, diffusely off-white, have an irregular capsular surface and may be enlarged up to three times their normal size. All renal components are susceptible and lesions may include tubular degeneration and dilatation, glomerular hypercellularity and hypertrophy (proliferative glomerulopathy), periglomerular fibrosis, lipid-laden cells within the glomeruli and multifocal, acute interstitial nephritis. Since only mortality and necropsy results were reported, clinical information such

as diagnosis and management/treatment were not provided. However, this does bring up the potential complication of feeding some birds high cholesterol foods.

High protein diets:
High protein diets have been associated with renal disease in birds, but only under specific conditions. Compared to a 'low-protein' diet group, pigeons fed a 'high protein' diet had an observed increase in drinking rates and urine production. Unfortunately, too little information was present to draw any conclusions relating dietary protein to renal disease. Chandra et al showed that feeding 18 day-old broiler chicks a 42.28% protein diet for 15 weeks did induce multiple renal abnormalities (primarily nephrosis and visceral gout). Extraordinarily high protein levels in the diet of genetically predisposed chickens have been shown to cause gout, but a direct relationship with renal disease has not been established. A more detailed discussion of the effects of dietary protein and hyperuricaemia are discussed under 'Diagnosis of Avian Renal Disease' and 'Treatment and Management of Avian Renal Disease'.

Diets high in urea have also been linked to nephritis outbreaks in poultry. Fish-meal adulterated with urea was linked to high (6-8%) mortality in two separate farms. Clinically affected birds had gross lesions that ranged from pale nephromegaly and hepatospenomegaly to urolithiasis and visceral gout. Histologic lesions ranged from interstitial, perivascular and pericapsular nephritis to proliferative glomerulopathy and severe tubular and glomerular atrophy and fibrosis in severe cases. The disease was termed 'nephritis-nephrosis syndrome in poultry' and was eliminated when the urea-adulturated feed was replaced with a different balanced diet.

'Diet-induced renal disease of color variety psittacine birds':
Although not formally entered into the veterinary literature, there appears to be a form of renal disease induced by feeding predominately pelletized diets to various color variety psittacine birds. All affected birds observed by the author have been color variety cockatiels (*Nymphicus hollandicus*), lovebirds (*Agapornis spp*.), budgerigars and parrotlets (*Forpus spp*.) and have eaten a predominately commercial pelletized diet. As most of the major brands of commercial pelletized diets have been involved, there appears to be no predilection towards any one manufacture's product. With the exception of a history of predominately commercial pelletized diet, affected birds do not display any characteristics pathognomonic for 'diet-induced renal disease'. Of the birds with suspected 'diet-induced renal disease', in which the kidneys have been histopathologically examined (pre- and postmortem), lesions have been limited to non-specific tubular nephrosis and were reversible after feeding a non-pelletized diet for one to three months. The diet should be converted to one appropriate for the species being treated.

Mycotoxic nephropathy:
Mycotoxic nephropathy, primarily due to ochratoxin A, has been reported in chickens and ducks. Ochratoxin A is produced by several species of *Aspergillus* and *Penicillium*. Ochratoxicosis occurs primarily because of ochratoxin A buildup in chick feed stored under conditions of excessive moisture and has been identified from mouldy feed, rice, groundnuts and foods prepared from these materials. Ochratoxicosis causes liver and kidney damage and specifically induces degeneration and vacuolation of hepatic cells and distension, enlargement and hypertrophy of renal proximal convoluted tubules, respectively. Because of the multiple potential sources of the toxin, it is reasonable to assume that multiple avian species, other than chickens and ducks, can be exposed to and damaged from ochratoxin.

Other mycotoxins have also been closely correlated with renal disease in birds. Oosporein, a toxic pigment produced by *Chaetomium trilaterale*, *C. aureum* and several other species of filamentous fungi, is considered to be primarily a renal toxin. The importance of oosporein is that the toxic isolates

have been found in various agricultural commodities such as animal feeds, cereal grains, and food products. Moldy corn in particular, growing *C. trilaterale*, may yield high concentrations of oosporein toxin. In studied young broiler chickens and turkey poults, oosporein toxicosis is dose dependant and can cause dehydration, stunted growth, pale nephromegaly and death and appears to severely affect uric acid secretion leading to hyperuricaemia and visceral and articular gout. Although still severely affected, turkey poults seemed to tolerate higher doses of oosporein before toxicosis was apparent than did broilers bringing up the issue of physiological differences between these two species. Sterigmatocystin (STG) is produced by multiple fungal species and has caused acute liver and renal disease and death in 10 to 12 day old leghorn chicks. Chicks given intraperitoneal STG developed tubular nephrosis and hepatic necrosis and died within 21 hours of injection.

Lead nephropathy:
Lead toxicity is the most common cause of metal poisoning in waterfowl and affects a wide variety of other bird species. Although neurological and gastrointestinal clinical signs are usually seen, lead can have severe effects on avian kidneys. Renal lesions may include proximal tubular necrosis and degeneration (nephrosis), visceral gout and in some birds, acid-fast intranuclear inclusion bodies. Kidney, liver and brain tissue concentrations of 3 to 6 ppm wet weight are suggestive and greater than 6 ppm is diagnostic for lead poisoning.

Congenital and hereditary defects
Multiple congenital renal defects are reported in birds. Heritable renal diseases such as X-linked hereditary nephritis in samoyed dogs and Alport's syndrome in humans are discussed with many mammals but poorly described in the current avian literature. In some large poultry flocks, up to 20% of the necropsied birds have had evidence of 'faulty kidneys' considered to be congenital in nature. Reported renal abnormalities include complete or partial kidney agenesis, ureteral dilitation, structural glomerular changes, and predilection toward hyperuricaemia (due to presumed proximal tubule defects). Renal cysts are occasionally seen and may be congenital or acquired. Polycystic renal disease has been noted in chickens, pigeons and a bald eagle (*Haliaeetus leucocephalus*). Renal agenesis is the most frequently described inherited defect and has been attributed to a simple recessive gene with variable penetrance in brown leghorn chickens. With partial renal agenesis, the cranial renal division is most likely affected. Although birds usually die with neurological signs or massive interrenal hemorrhage, emus (*Dromaius novaehollandiae*) with inherited neuronal storage disease (gangliosidosis) develop unusual large vacuoles in the renal tubular epithelial cells of the proximal convoluted tubules. Congenital renal diseases have been reported in chickens, pigeons, quail, a canary and a Mandarin duck but likely exist in numerous other species.

Fatty associated diseases
Lipids are not histologically evident in normal avian renal tissue but may be noted under certain pathologic circumstances. Fasting (water and food) may result in reversible lipid deposition within the renal tubular epithelium. Defects in lipid metabolism or storage may also account for renal tubule cell lipidosis.

The now rare, fatty liver and kidney syndrome of broiler flocks and turkeys (due to biotin deficiency) can cause heavy lipid accumulation within the proximal convoluted tubules. At necropsy, the liver, kidneys and sometimes other organs are often pale and swollen with deposition of sudanophilic lipid droplets.

A fatty liver-kidney syndrome has also been reported in merlins (*Falco columbarius*). Only captive birds have been affected. Most affected merlins have been approximately 5% above normal body weight and fed a diet predominately of day-old chicks for several months prior to death. Most affected merlins died suddenly either while eating or with the keeper. A few become lethargic for a few hours

before death. As is seen in broiler chicks, merlins with fatty liver-kidney syndrome develop excess fat in the liver, kidneys and spleen. Day old (feeder) chicks contain appreciable avidin, which may bind dietary biotin, in turn leading to (a theoretical) biotin deficiency. Biotin and other deficiencies, high fat diet, hepatic anoxia and various toxic agents, have been proposed as causes of fatty liver-kidney syndrome of merlins, but a definitive aetiology has not been confirmed.

Neoplasia

The avian kidney, just as with other animal tissue, is susceptible to neoplastic conditions. Nephroblastomas are the most commonly reported avian renal tumor. Nephroblastomas and renal adenocarcinomas comprise the majority of kidney tumors in budgerigars (*Melopsittacus undulatus*). Renal carcinomas are the most frequently reported tumor of the urinary system in non-domestic free-ranging and captive birds. Malignant renal tumors are more commonly seen in males than females and are more commonly observed in psittacine than passerine species. In one study of 74 budgerigars suspected of having ceolomic tumors, one-legged lameness and abdominal enlargement were the primary clinical signs. In the same study, 47 birds (63.5%) had renal tumors and were diagnosed most commonly within 5 years of age.

Lymphoid, myeloid and erythroleukaemias, lymphoma, ovarian, liver, and oviductual adenocarcinomas, hemangioma, lipoma, histiocytic cell sarcoma, neurofibroma, granulosa cell tumor, cystadenoma with bone, squamous cell carcinoma, unclassified carcinoma and osteogenic sarcoma have all been reported as either primary or secondary renal neoplasms in birds.

Like other cancers, there are likely many causes of renal tumors in birds but there is little information regarding definitive etiologies. Avian leucosis virus (ALV) can induce renal tumors in chickens. While ALV has been found in budgerigars with renal tumors, a definitive association has not been made.

A common presentation with renal cancer is unilateral to bilateral leg weakness or paralysis and slight ataxia. Other clinical signs may vary but often include diarrhea, dyspnea, abdominal distension and weight loss.

The lumbar plexus lies dorsal to the cranial renal division while the sacral plexus runs through the middle division parenchyma. Because of this close association, any parenchymal inflammation or pressure on, or from within, the kidney can potentially result in nerve dysfunction and resultant lameness. Additional neoplastic extension to the overlying spinal column may also result in nerve dysfunction. Peripheral neural compression should result in peripheral neuropathy with eventual loss of the withdrawal reflex, not seen with most spinal cord lesions. In addition to lameness and muscle atrophy, ipsilateral osteopenia was noted in a cockatiel (*Nymphicus hollandicus*) with a renal adenocarcinoma.

Unfortunately, avian renal tumors carry a poor prognosis. In reported cases of renal cancer, most birds lived less than 3 months following diagnosis. Van Toor et al stated in reference to budgerigar renal tumors that ‘the course of the disease may take weeks to several months.’.

Urolithiasis and ureteral obstructive disease

In birds, urolithiasis refers to the ‘formation of large urate “stones” in the ureters’, is primarily seen in pullets and caged laying hens and can result in increased mortality and decreased egg production. Urolithiasis has been reported primarily in the poultry literature on numerous occasions, but is rarely described in other avian species.

Common findings include atrophic ispsilateral renal tissue, a normal to hypertrophic (compensatory)

contralateral kidney and a dilated ureter obstructed with one or more urate stones. Histologic lesions noted with urolithiasis have included glomerular nephritis, tubular nephrosis, ureteritis and 'pyelonephritis' with interstitial mononuclear infiltrates. One study noted that 'virtually every cull hen or out-of-production hen examined at affected layer complexes (sites with high incidences of urolithiasis) had gross kidney lesions and kidney stones'. In birds, ureteral obstruction (as may occur with ureteroliths, cloacal masses, urodeal fold thickening, etc) may cause a post-obstructive form of renal disease. Simple ligation of a bird's ureter results in ipsilateral renal atrophy and this result is similarly expected with urolithiasis. Naturally occurring ureteroliths in chickens are known to contain uric acid, urates, calcium and ammonia. These statements suggest that the kidney should be closely evaluated (via biopsy, for example) when urolithiasis is present.

The cause of urolithiasis in poultry flocks has not been definitely identified. However, it is known that coronavirus-associated nephritis in pheasants can induce interstitial nephritis, tubular dilatation, ureteral impaction and subsequent visceral gout. In addition to infectious bronchitis virus infection (IBV, a coronavirus), other proposed causes or urolithiasis in poultry include water deprivation, excess dietary calcium and nutritional electrolyte imbalances. One group reported that by changing the form of calcium from small particle size to flakes, adding additional phosphorous and by modifying the IBV vaccination protocol, the investigators were able to significantly reduce the incidence of urolithiasis in a previously affected layer flock. However, they could not determine which management change resulted in the beneficial effect.

Urolithiasis in psittacine species is rare, but has been reported. A 21-year-old male double-yellowheaded Amazon parrot (*Amazona ochracephala*) with a history of straining to void lifelong and chronic intermittent vomiting for a 'few years' was diagnosed with septic ureteral fluid and ureterolithiasis. Dorsocaudal coelomic radiodense opacities were noted on screening radiographs, but the diagnosis was ultimately made via exploratory ceolomotomy. Multiple surgeries were required to remove the stones. A kidney biopsy was not collected and a relatioship to renal disease could not be made. The ureteroliths were composed of 'monosodium uric acid crystals and proteinaceous material mixed randomly or forming irregular laminae'. Although the bird had dry flaky skin, a urate pasted vent, dull feathers and heterophilic (28,840 cells/µl) leukocytosis (32,000 cells/µl), the authors concluded that the clinical signs associated with ureterolithiasis in this bird were non-specific and may result in delayed diagnosis. The cause was not determined.

Amyloidosis

Amyloidosis is occasionally noted in association with avian renal disease. Amyloid deposits are often related to chronic inflammatory disease and usually found systemically, but can affect specific tissues. Typically amyloid presents histologically as amorphous, eosinophilic, homogenous material that stains red-orange with Congo red and bright green when examined under polarized light. Amyloidosis is most frequently noted in captive Anseriformes (geese, ducks, swans), Gruiformes (cranes) and Phoenicopteriformes (flamingos), but has also been reported in numerous other species.

There are a few reports of amyloidosis involving the kidneys of birds. Multifocal amyoidosis was noted in a diamond firetail finch (*Stagnoplura bella*) with proventricular cryptosporidiosis and was found specifically in the glomeruli and interstitial tissue around the tubules. Numerous laying Japanese quail with systemic amyloidosis had amyloid deposits in the renal tubules and no to minimal deposition in the glomeruli. While some of the birds had concurrent inflammatory diseases, such as egg yolk peritonitis, the aetiology` of the amyloidosis was not determined. Four days after acute onset illness, a roseate flamingo (*Phoenicopterus ruber*) died with necrogranulomatous and septic air sacculitis, perihepatic serositis and hepatic capsulitis, hemosiderosis, atherosclerosis and systemic amyloidosis. The renal amyloid involvement was severe resulting in a marked glomerulopathy and was likely the cause of death. Amyloid was found within the connective tissue of mycobacterial

tubercles found on the kidney surface of a hooded merganser (*Lyphodytes cucullatus*). No details were given regarding the pre-mortem disposition of the bird. The author has noted renal amyloidosis in pet geese. These birds presented in end-stage renal failure and necropsy showed severe renal amyloidosis. The underlying cause was never elucidated.

Renal hemorrhage

Renal hemorrhage is sporadically reported in the literature and may exist predominantly as a secondary finding. Sudden death syndrome (SDS), also known as 'perirenal hemorrhage syndrome', is the main cause of death in heavy turkey flocks from 8 to 14 weeks of age. Primarily male turkeys in good body condition die acutely with SDS and typically have characteristic post-mortem lesions including perirenal hemorrhage and organ congestion including the lungs, spleen and liver. One group noted that most affected birds had hypertrophic cardiomyopathy and proposed that acute congestive heart failure was the cause of death and severe passive congestion accounted for the perirenal hemorrhage. The cause is still unknown but other theories include severe lactic acidosis and limited cardiac capacity, noted in predisposed turkeys, as contributing factors.

An adenovirus, new gosling viral enteritis virus (NGVEV) has been shown to cause renal hemorrhage and hyperaemia 4 days post-infection in newly hatched goslings. Renal tubular and ureteral epithelial cell degeneration and intestinal glandular epithelial cell necrosis and sloughing were also consistently seen in the goslings infected with the rapidly progressive NGVEV.

Hydropericardium syndrome of broiler chickens is a contagious disease caused by an adenovirus and can result in grossly swollen kidneys with extensive renal hemorrhage and hydropericardium. Three to 6 week-old broilers are typically affected and mortality ranges from 10 to 60 percent. Renal tubular nephrosis and necrosis within the liver, spleen and bursa of Fabricius may be seen microscopically.

Other causes of renal hemorrhage may also be seen. Simple trauma, such as from an animal bite or endoscopic biopsy, may result in renal hemorrhage. If the renal capsule is left intact, a subcapsular hematoma may form increasing the renal size and possibly place pressure on the neighboring nerve plexi. Renal petechial hemorrhage resulting from *Clostridium perfringens* toxaemia was reported in a rock partridge (*Alectoris graeca*).

Metabolic renal disease

Metabolic renal disease includes dehydration, diabetes mellitus, amyloidosis, gout and lipidosis, the latter three of which have already been discussed. Diabetes mellitus has been noted in a variety of birds and is seen with polyuric, polydipsic glucosuria and hyperglycaemia. Descriptions of the gross and microscopic effects of diabetes mellitus on avian kidney tissue were not found.

One of the more common metabolic derangements associated with renal disease is dehydration. In chickens, dehydration has been associated with nephrosis characterized by tubular dilatation, with or without proteinaceous casts, epithelial necrosis and rare urate granulomas or casts. Food restriction during dehydration may lessen the nephrosis lesions.

Gross renal changes

Gross renal changes including masses, discolorations and size and shape alteration are non-specific and should be cautiously interpreted.

Differential diagnoses for renomegaly include neoplasia, inflammation (including infectious and non-infectious diseases), cystic formation, ureteral obstruction, toxic changes, metabolic disorders (including dehydration, gout, lipidosis) and congenital abnormalities. Also, non-pathological increase in kidney size has been noted in chickens fed certain dietary precursors, such as inosine, that increase

plasma uric acid levels. In these chickens, the renal enlargement was likely due to the increase in processing of uric acid in the kidney. Renal and ureteral calculi may also be noted.

Post-mortem renal change

Renal post-mortem changes are noted in chickens as soon as 22 minutes following death at 37°C (98.6°F). Early renal post-mortem changes occur in the proximal tubular epithelium, followed by collecting tubule epithelium and glomerular nuclei. Even with cooling to 4°C (39.2°F), proximal tubular changes can be observed within 45 minutes of death. The early post-mortem proximal tubular changes can be confused with antemortem proximal tubular degeneration and should be interpreted with caution. In order to decrease post-mortem changes, perform a necropsy and fix tissues as soon as possible after death.