

CHAPTER

21

NEPHROLOGY

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Confirming a diagnosis of renal disease in birds is often difficult because clinical signs are generally nonspecific and are frequently complicated by secondary changes caused by renal dysfunction. Lethargy, with a diminished appetite leading to emaciation, is typical of renal disease. Birds may appear unable to fly, while in reality they are too weak to fly. A distended abdomen with or without ascites may be seen with renal tumors. In over 50% of renal neoplasms, the tumor can be palpated (Color 21.11).² Renal masses and ascites may prevent normal air flow and cause dyspnea because of compression on the abdominal and caudal thoracic air sacs (Color 21.4). Urinary output may vary from anuria to polyuria. In oliguric patients, the possibility of acute nephrotoxic renal failure should be considered, and the client should be carefully questioned concerning the administration of nephrotoxic drugs (eg, allopurinol, aminoglycosides, polypeptide antibiotics and sulfonamides) or exposure to sodium chloride (eg, saline as drinking water, sea sand for bedding material, heavily salted foods) or other nephrotoxic substances (eg, heavy metals, ethylene glycol, carbon tetrachloride).

Clinical findings can be quite suggestive of renal disease. During the physical examination, signs of dehydration or shock may suggest a diagnosis of prerenal renal failure. Dehydrated birds have a reduced skin elasticity and dry mucous membranes. Subcutaneous urate tophi or urate accumulations in joints are signs of articular gout (Color 21.3), a clinical sequela to hyperuricemia, which in birds is caused by a renal disorder. Unilateral or bilateral paresis of the legs is often the first clinical sign of renal neoplasm in psittacine birds (particularly budgerigars). Neurologic signs are seen in about one-third of renal neoplasms, but may also be caused by other space-occupying lesions in the ipsilateral kidney (eg, iatrogenic hematoma, renal aspergillosis) (Color 21.2). Neurologic changes are secondary to compression or inflammation of branches of the lumbosacral plexus, which pass through the kidneys (Color 21.1). Constipation may also occur if the renal mass compresses the large intestine. In large birds, a lubricated, gloved finger can be inserted and moved dorsally in the cloaca in order to palpate the caudal division of the kidney. Any swelling, asymmetry or tenderness may be an indication of renal disease.⁴

Clinicopathologic changes in the blood and urine depend on location and severity of the renal lesions (eg, glomerulopathies may lead to severe protein loss and hypoalbuminemia, while tubular lesions may lead to hyperuricemia or polydipsia).

Anatomy and Physiology of the Kidney

The paired kidneys are located dorsally in a depression of the pelvis. Each kidney is made up of three divisions that are frequently referred to as lobes (cranial, middle and caudal). The divisions are composed of lobules with a large cortical mass and a small medullary mass. It is difficult to demarcate between the cortical and medullary portions of the lobules. The cortex is composed of both reptilian-type nephrons that do not contain loops of Henle and mammalian-type nephrons that do contain loops of Henle. The reptile-type nephrons are most numerous, and birds are less efficient in the excretion of electrolytes than mammals. The cortical-type nephrons are uricotelic and the medullary-type produce urine. The former are located on the surface of the kidney, and the latter are located in a deeper orientation. The nephrons' collecting ducts and ureters are contiguous. The kidneys of birds are larger by weight than in mammals. There are three pairs of renal arteries. The anterior branch arises from the aorta, and the middle and posterior branches arise from the sciatic artery or external iliac artery. The anterior branch supplies the cranial division of the kidney, and the middle and posterior branches supply the middle and caudal divisions of the kidney.

Birds have a renal portal system in which the renal portal vein functions like an artery by carrying blood to the tubules. Flow of blood into the kidneys from the renal portal system is controlled by valves. These valves are bilateral and are located at the junction of the external iliac vein and the renal vein. Studies suggest that acetylcholine causes the valves to close and epinephrine causes them to open. If agents excreted by the renal tubules are injected into the legs, they are excreted by the tubules on the injection side of the body before entering the general circulation.

Glucose is completely filterable and is normally absorbed by the kidney. Glucosuria indicates that renal absorption is damaged or that excessively high levels of glucose are being presented to the kidneys. The avian kidney has a reduced capacity to secrete creatinine in comparison to uric acid.

Renal output varies with the water intake and stress levels of the bird, but is generally considered to be 100 to 200 ml/kg/day. By comparison, dehydrated birds may have a renal output of 25 ml/kg/day. There is a physiologic polyuria that occurs a few hours before egg laying.

Some urine water that is excreted into the cloaca is passed by antiperistaltic movement of the cloaca into the colon where absorption of the liquid occurs. In dehydrated birds, 15% of urine water may be reabsorbed from the colon. The amount of water absorbed by the colon is decreased with polyuria or with a stress-induced defecation creating a moist-appearing excrement.

Pathophysiology

Etiology of Gout

Uric acid (UA) is produced in the liver and is the major end product of deamination of amino acids in birds. It constitutes approximately 60 to 80% of the total excreted nitrogen in avian urine. Uricotelism permits excretion or storage of nitrogen waste in a small volume of water. Uric acid is relatively nontoxic when compared to urea or ammonia. This method of handling nitrogenous waste is essential for embryo development within an egg. Uricotelism may also be viewed as an adaptation for water conservation.

Uric acid is synthesized in the liver. Ninety percent of its excretion is via tubular secretion from reptilian-type nephrons and therefore largely independent of urine flow rate. The clearance of uric acid surpasses the glomerular filtration rate by a factor of eight to sixteen and is occasionally even higher. The rate of secretion is largely independent of the state of hydration because UA excretion is independent of tubular water reabsorption. Very high concentrations of uric acid can be found in ureteral urine in dehydrated birds. Renal function disorders can eventually lead to elevated uric acid concentrations. However, non-protein nitrogen substances in plasma, such as uric acid, creatinine and urea will be elevated only when renal function is below 30% of its original capacity.

Hyperuricemia is defined as any plasma uric acid concentration higher than the calculated limit of solubility of sodium urate in plasma and is an indication of nephrosis or impaired renal function. An ordinary aqueous solution at 37°C, with a sodium concentration equal to that of normal human plasma is saturated when the urate concentration reaches 383 to 407 $\mu\text{mol/l}$. It is generally accepted that the upper limit of solubility of urate in human plasma, is 420 $\mu\text{mol/l}$.³ Urate solubility increases with higher sodium concentrations and higher temperatures. When the higher body temperature of birds (up to 43°C) is taken into account, the theoretical limit of solubility would be about 600 $\mu\text{mol/l}$. Because avian species have a higher plasma sodium concentration than humans (136-145 mmol/l), the theoretical limit of urate solubility is even higher. Hyperuricemia can result in urate precipitation in joints (articular gout) (Colors 21.10 and 21.12) and in visceral organs or other extra-visceral sites (visceral gout) (Color 21.7). The exact mechanism of deposition or the predilection for gout to occur in certain sites is unknown. Gout should not be regarded as a disease entity, but as a clinical sign of any severe renal dysfunction that causes a chronic, moderate hyperuricemia.

When birds are provided with dietary protein in excess of their requirements, the surplus protein is catabolized and the nitrogen released is converted to uric acid. The total amount of uric acid formed may surpass the clearing capacity of this substance from the body, and hyperuricemia and articular gout may result. The use of high-protein poultry pellets as the bulk food in psittacine aviaries may result in an increased incidence of gout (See Chapter 3).

- **Articular and Visceral Gout** There is no consensus on the different etiologies of articular and visceral gout in birds. The following hypothesis seems to explain all known facts.

A plasma uric acid concentration that is slightly above the solubility of sodium urate will lead to uric acid precipitation in the body. Predilection sites are those areas where the solubility of sodium urate, for whatever reason, is lower than in other areas (Figure 21.1). The joints and synovial sheaths may be predilection sites because of a lower temperature than the rest of the body. Once uric acid deposits have occurred in a specific area, these deposits will grow with time, forming tophi (accumulations of uric acid) (Color 21.8).



FIG 21.1 A six-year-old male budgerigar was presented for lameness of several days' duration. Multiple, firm, raised nodules (tophi) were noted at several periarticular locations. The severe articular gout was considered unresolvable and the bird was euthanized. Histopathology revealed severe nephritis.

If, for whatever reason, uric acid crystals precipitate in the tubules or collecting ducts of the kidney (eg, severe dehydration of long duration, hypovitaminosis A) or the ureters, an acute obstructive uropathy (postrenal obstruction) will occur (Color 21.3). These birds develop anuria or gross oliguria, and tubular secretion of uric acid is severely compromised or stops. This results in a rapid and severe elevation of plasma uric acid concentration with precipitation of urates on many visceral surfaces, including those predilection sites for articular gout. Visceral gout will rapidly lead to death of the affected animal. This hypothesis is supported by the fact that inflammation and tophi formation are rare with visceral gout, because the condition has a rapidly fatal course. There is simply no time for an inflammatory reaction or tophi to develop. The kidney tubules, collecting ducts and ureters may contain uric acid deposits.

Acute, renal tubular failure, which would lead to acute abolishment of uric acid secretion, would result in a similar course of events. In this situation, visceral gout could develop without uric acid deposits forming in the tubules, collecting ducts and ureters.

The acute mortality seen in birds with visceral gout is probably not due to the effects of hyperuricemia, because uric acid is generally a nontoxic, insoluble substance. It is likely that these birds die from cardiac arrest caused by hyperkalemia, although this hypothesis needs confirmation.

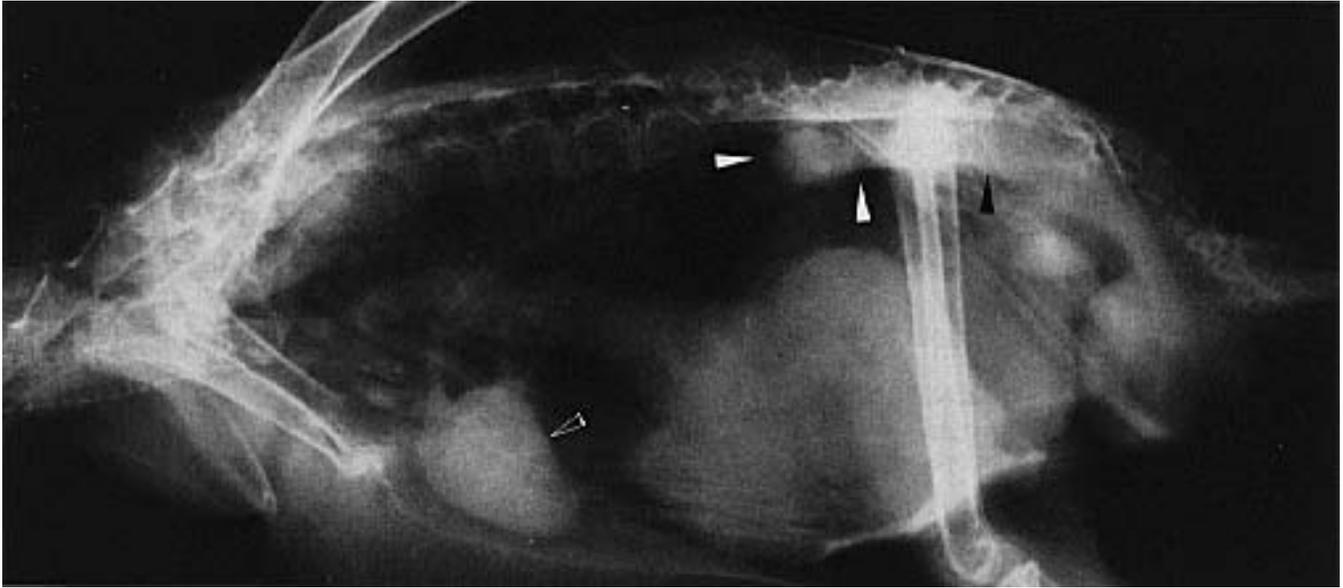


FIG 21.2 An adult male Umbrella Cockatoo was presented with severe depression, emaciation (470 g) and putrid, watery diarrhea. Abnormal clinical pathologic findings included WBC=46,000, PCV=34%, TP=7.5 and LDH=500. Radiographic lesions included a microcardia (open arrow) and radiodense kidneys (arrows), both of which are indicative of dehydration and hypovolemia. Necropsy findings included small irregular kidneys with multiple granulomas and granulomatous tubulointerstitial nephritis.

Acute and Chronic Renal Failure

Renal dysfunction may result from any progressive destructive condition affecting both kidneys (chronic renal failure), but can also occur in conditions wherein the function of the kidneys is rapidly and severely, but often reversibly, compromised (acute renal failure) (Figure 21.2). In the latter condition, oliguria usually occurs, while in the former situation, polyuria is normally seen. Dehydration and shock (prerenal renal failure), urolithiasis (postrenal renal failure) and urinary tract infections and the administration of nephrotoxic drugs can all cause changes that mimic irreversible chronic renal failure. Appropriate and timely treatment of the former conditions can often prevent further damage and in some cases result in improved function. Extrarenal factors such as infection, gastrointestinal hemorrhage and hypovolemia can disturb an otherwise stable, well compensated, asymptomatic patient with chronic renal disease and precipitate a life-threatening, acute clinical change.

Prerenal Azotemia

Prerenal azotemia can be defined as the clinical condition associated with reduced renal arterial pressure or perfusion leading to oliguria and retention of

nitrogenous urinary waste products in the blood. It is often seen during shock or severe dehydration. In clinical textbooks, it is commonly stated that dehydrated birds have elevated plasma uric acid concentrations. In recent experimental studies, elevated plasma uric acid concentrations were not observed in racing pigeons that were deprived of water for four days, while plasma urea concentration showed a significant 6.5- to 15.3-fold increase above reference values. Urea is normally present in low concentration in avian plasma and determination of this has traditionally been considered of little value in evaluating renal function in birds; however, plasma urea appears to be the single most useful variable for early detection of prerenal causes of renal failure (dehydration).²¹

These observations can be explained by the fact that urea is excreted in the kidneys by glomerular filtration, while tubular reabsorption is dependent on tubular urine flow, which in turn depends on the state of hydration. In a hydrated bird, almost all of the filtered urea is excreted. When a bird is dehydrated, nearly all of the filtered urea is reabsorbed. The tubular reabsorption of urea in conditions of renal failure, accompanied by a low urine flow (eg, dehydration) in combination with a nearly unchanged excretion of uric acid, causes a disproportionate increase in plasma urea concentration, which results in an elevated urea:uric acid ratio.

Chronic, progressive dehydration may eventually lead to hyperuricemia. This might be caused by reduced tubular blood supply that leads to reduced uric acid secretion or by uric acid precipitation in the tubuli caused by active tubular secretion of uric acid in the absence of urine flow. The latter condition appears similar to acute uric acid nephropathy described in man.

Postprandial Effects

It has been demonstrated that a significant postprandial increase in plasma uric acid (UA) and urea concentration occurs in Peregrine Falcons and Red-tailed Hawks.^{24,25}

Postprandial plasma UA levels were similar to those in birds suffering from hyperuricemia and gout and were well above the theoretical limit of solubility of urate in plasma. It is not clear why at least twelve hours of postprandial hyperuricemia does not result in uric acid deposition in the tissues. The fact that Peregrine Falcons have relatively high plasma sodium concentrations might partially explain their

tolerance of high plasma UA levels. In order to prevent misinterpretation of high plasma UA levels caused by the ingestion of food, it is recommended that repeat samples be evaluated following a fasting period in any bird that initially has a high plasma UA or urea concentration.

Evaluation of Urate Tophi

Macroscopically, the aspirated material from articular gout looks like toothpaste (Color 21.10). The presence of urate can be confirmed by performing the murexide test or by microscopic examination of aspirates from suspected tophi. The murexide test is performed by mixing a drop of nitric acid with a small amount of the suspected material on a slide. The material is dried by evaporation in a flame and allowed to cool. One drop of concentrated ammonia is added, and if urates are present, a mauve color will develop. Microscopically, sharp, needle-shaped crystals can be seen in smears. A polarizing microscope is helpful in identifying the typical crystals.

Blood Changes

Apart from elevated concentrations of nonprotein nitrogen substances, a number of other variables are known to change in mammals as a result of acute or chronic renal failure. Hyperkalemia, which may lead to severe electrocardiographic changes and cardiac arrest, is a particular problem in acute renal failure. Hyperkalemia (5.2 mmol/l) was described in a Red-tailed Hawk with acute renal failure.²⁴ In man, plasma potassium concentration can be lowered promptly and for a number of hours by infusion of one liter of 10% glucose solution containing 10 to 20 IU insulin; however, in birds, insulin may cause acute hypoglycemia, CNS swelling and death. Infusion of 10% calcium gluconate solution may reverse the cardiotoxic effects of severe hyperkalemia without affecting plasma potassium concentration. Hypocalcemia and hyperphosphatemia are common in mammals with renal failure. The former may lead to hypocalcemic tetany, especially with rapid correction of acidosis. Because these variables have significant therapeutic implications, documentation of their occurrence in avian renal disease is necessary. Anemia has also been documented in birds with chronic renal failure.

Clinicopathologic Diagnosis of Renal Dysfunction

Urinalysis

Analysis of urine has been shown to be a valuable diagnostic tool in veterinary medicine. Examination of urinary sediment and determination of urinary protein concentration are the most valuable procedures in the differential diagnosis of renal diseases. Renal function tests provide information on the degree of functional impairment. Urinalysis may give an early warning of renal damage or impaired renal function long before there is an increase in plasma nonprotein nitrogen concentrations. Signs of renal damage or impaired renal function include proteinuria, glucosuria without hyperglycemia and casts or cells in urinary sediment.

Despite its high diagnostic value, urinalysis is not routinely performed in avian medicine, perhaps because it seems difficult to separate urine from feces. Practical guidelines for urinalysis in companion birds have been developed and are an indispensable part of the diagnostic workup in polyuric birds.^{38,39} The identification of casts in urinary sediment is strongly suggestive of renal disease. In polyuric cases, collection of a urine sample is relatively simple and can be performed by aspirating the fluid part of the excreta into a syringe from a clean enclosure floor covered by wax paper. It is important that the urine sample be relatively free of urates to ensure the diagnostic value of microscopic examination of the sediment. Sediments obtained from the total renal fraction of the excreta will contain excessive urates; the results are of limited diagnostic value. Clinically normal birds have a tendency to become polyuric when in a stressful environment (eg, the veterinary clinic). In these birds, a urine sample is easy to obtain because of the bird's tendency to increase the frequency of cloacal emptying when nervous (Color 21.13). This will result in the excretion of urine fraction that has not moved retrograde into the large intestine where absorption of water and salts typically occurs.

Urate-free urine samples should be examined for specific gravity or osmolality, color, clearness, pH, protein, glucose, hemoglobin and the sediment should be examined microscopically.

Several methods for collecting avian urine from non-polyuric birds have been reported. The modified cloacal cannula method^{5,15} is the most appropriate for clinical use in docile birds (eg, racing pigeons) because it is the least invasive and is useful under clinical conditions. Reference values for twelve chemical and physical variables established in supernatants of pigeon urine (7000 G for 2 minutes) collected with the cloacal cannula method have been established (Table 21.1) and might provide a new perspective for the application of urinalysis in avian medicine.

TABLE 21.1 Reference Values (P_{2.5}-P_{97.5}) for Pigeon Urine¹⁵

Variable	Reference Values (SI units)
Urine production	2.3-19.7 ml/kg/h
Osmolality	27-193 mOsmol/kg
Flow-osmol factor	237-1847mOsmol/ml/kg/h
Glucose	0-3.2 mmol/liter
Total protein	0.11-1.99 g/liter
Uric acid	1.2-10.1 mmol/liter
pH	5.5-6.9
Na ⁺	2.0-27 mmol/liter
K ⁺	4.0-27 mmol/liter
Inorganic P	0.2-10.9 mmol/liter
Cl ⁻	5.0-56 mmol/liter
NH ₄ ⁺	4.6-39.5 mmol/liter

Osmolality and Specific Gravity

The low urine osmolality as reported in Table 21.1 can be explained by the fact that birds can produce urine with a considerably lower osmolality than the osmolality of blood plasma, due to the presence of reptilian-type nephrons as well as mammalian type nephrons.^{29,44} High urine osmolalities are common in avian species that are adapted to desert situations (Zebra Finch and budgerigar). Budgerigars can survive long periods (up to a month) without water under certain conditions;⁴¹ however, domesticated budgerigars and finches that are provided free-choice water may lose much of their compensatory ability. Maximum urine osmolalities in birds vary from 500 to 1000 mOsmol/kg.⁴¹ The emu is adapted to the Australian semidesert and has a low turnover rate of water, but has a limited renal concentrating ability with a maximal urine:plasma osmotic ratio of only 1.4:1.5. In this species, the large intestine has been adapted to preserve water. The high resorptive capacity may be related to increased folding of the mucosal surface, which increases the surface area by a factor of five.⁴³

■ Nephrology

Color 21.1

In health, the kidneys are dark red-brown and consistent in color. Cranial (k1), middle (k2) and caudal (k3) divisions of the kidney adhere tightly to the synsacrum in the dorsal abdominal wall. The right kidney has been removed to show the relationship of the kidneys with the synsacrum (s) and the sacral nerve plexus (arrow). Other structures that are easily identified include the lung (lu), left ovary (o) and oviduct (open arrow).

Color 21.2

A Black Palm Cockatoo with a history of progressive rear limb ataxia died and was presented for necropsy. The walls of the left abdominal and caudal thoracic air sacs were thickened, and a velvet-like yellow material was present on the surface of the membranes (arrow). The cranial and middle divisions of the left kidney and the ischiatic nerve (open arrow) were also involved. Aspergillosis air sacculitis with extension to the kidneys and nerves was the cause of death in this bird.

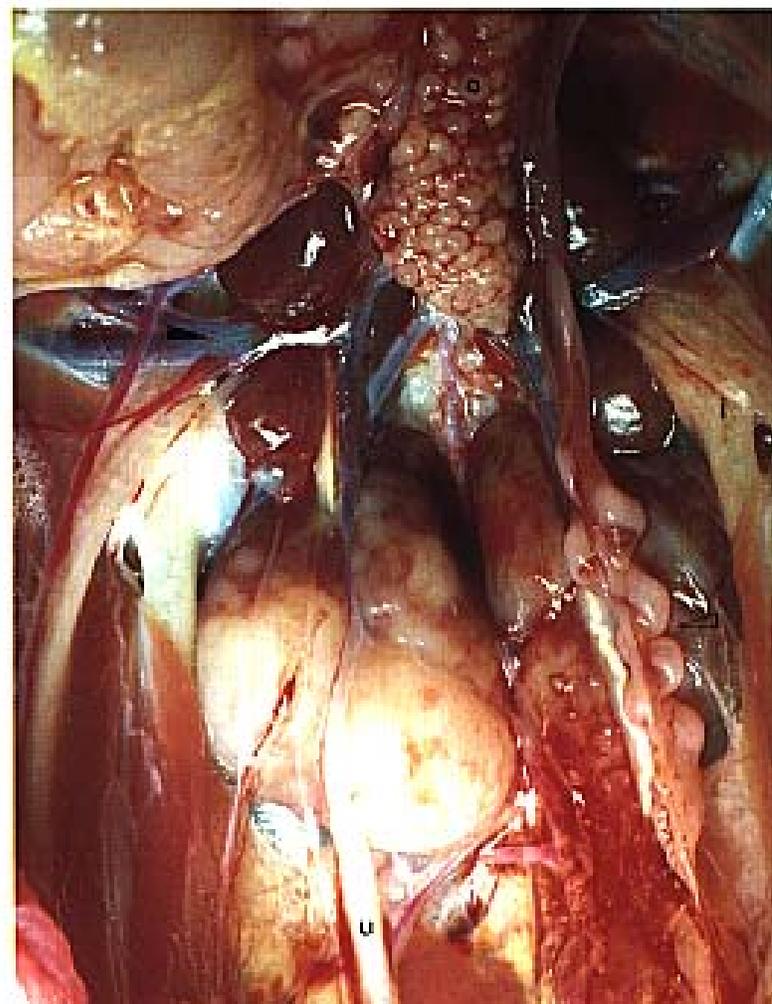
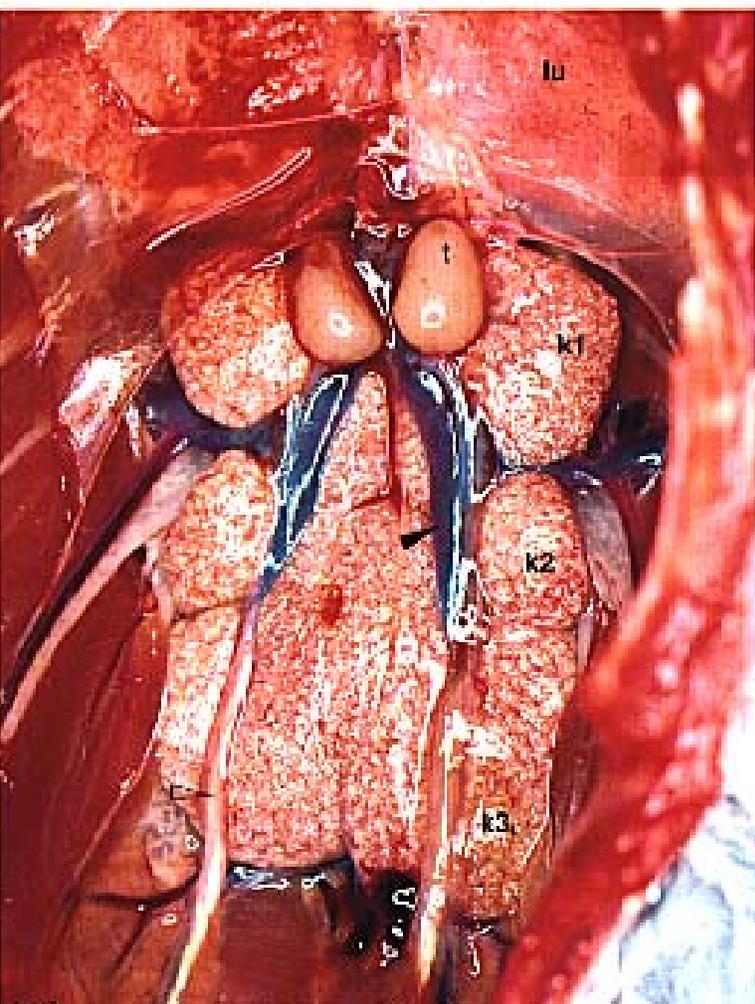
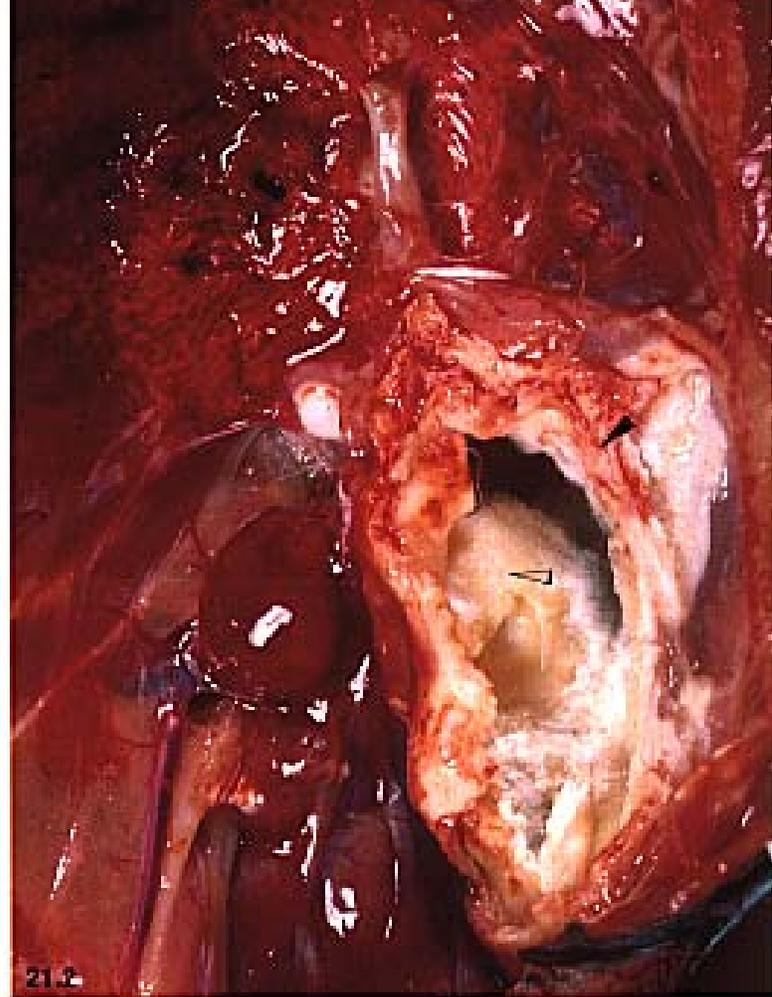
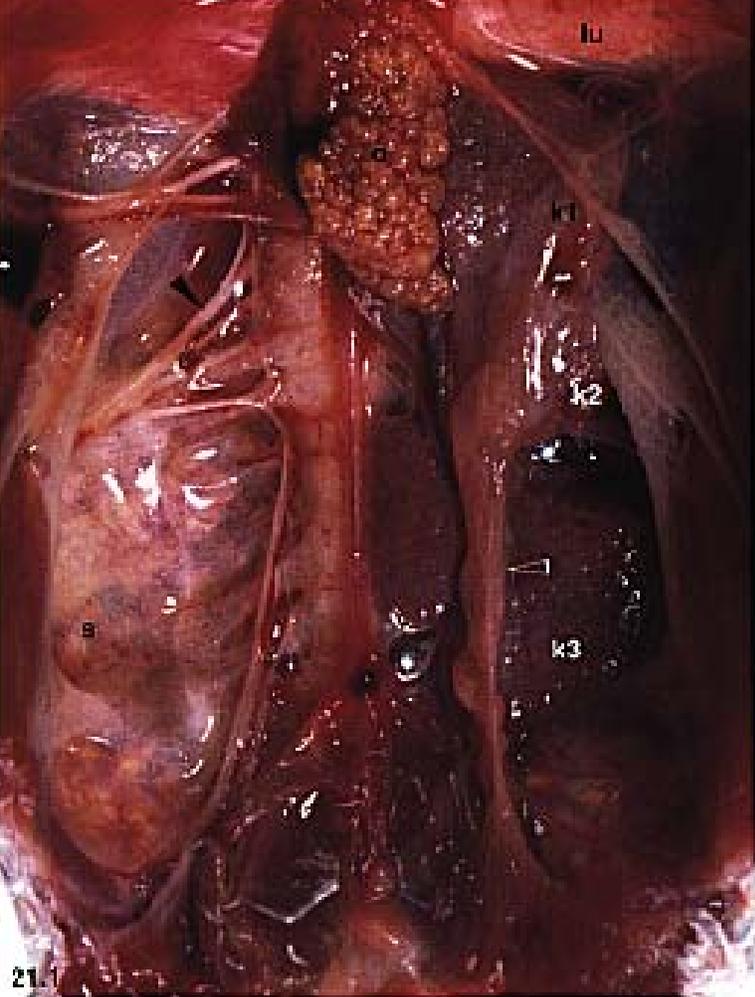
Color 21.3

Birds with decreased renal function may develop uric acid deposits (gout) in visceral organs or in joints. The linear white streaks

within the renal parenchyma in this African Grey Parrot are characteristic for gout. This was a breeding male that died after a brief period of severe depression. Uric acid deposits were also present in the pericardium and liver (see Color 21.7). Structures that are clearly visible are cranial (k1), middle (k2) and caudal (k3) divisions of the kidney, right and left testicles (t), lung (lu), ureter (open arrow), caudal renal vein (arrow).

Color 21.4

A mature, female African Grey Parrot was presented for evaluation of severe dyspnea. Radiographs indicated a large mass in the left thoracic cavity. Histologic evaluation of a fine-needle aspirate was suggestive of adenocarcinoma in the lung. A renal mass identified at gross necropsy was confirmed to be a renal adenocarcinoma. This bird had no clinical changes suggestive of rear limb ataxia or weakness, which frequently accompany renal masses. The ovary (o), oviduct (open arrow), ischium (i), external iliac vein (arrow) and ureter (u) are clearly visible.

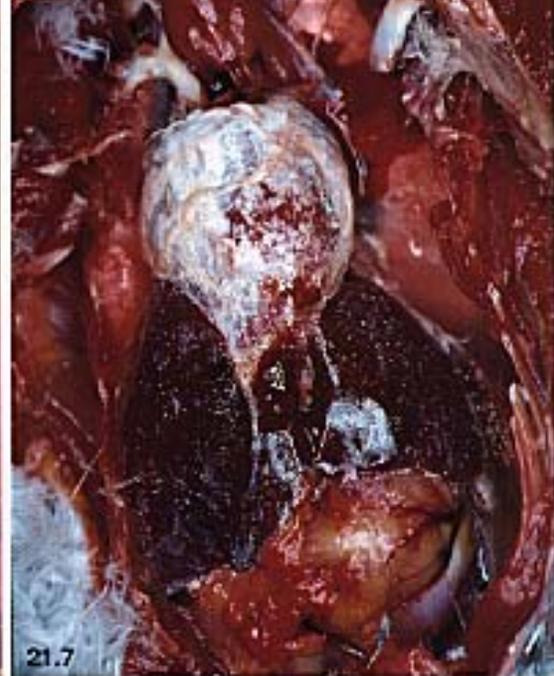




21.5



21.6



21.7



21.8



21.9



21.10



21.11



21.12



21.13



21.14



21.15

Nephrology

Color 21.5

Hemorrhage and swelling of the right cranial division of the kidney (arrow) in a juvenile Umbrella Cockatoo. The left kidney (k) is unusually pale.

Color 21.6

Iron storage disease is a common cause of death in toucans and mynahs. Excessive accumulation of iron is usually present in the liver but can also occur in the kidney (k), as seen in this toucan. These affected kidneys are swollen and orange in color. Other structures that are clearly visible include the ovary (o), oviduct (arrow) and the caudal renal vein (open arrow) (courtesy of Robert E. Schmidt).

Color 21.7

Deposits of uric acid in the pericardium and liver of an African Grey Parrot with renal failure (see Color 21.3).

Color 21.8

Gout in a five-day-old rhea chick. Note that the tubules are white and filled with urates (courtesy of Brett Hopkins).

Color 21.9

Gout in a five-day-old rhea chick. Note that the tubules are white and filled with urates (courtesy of Brett Hopkins).

Color 21.10

A mature pigeon was presented for lameness and an inability to fly. Prior to dissection, the firm, white, periarticular masses could be visualized through the skin (as in Color 21.12). Cytology of material collected from the masses revealed numerous uric

acid crystals. Articular gout is common in some birds secondary to renal dysfunction.

Color 21.11

A three-year-old budgerigar was presented with a two-week history of progressive ataxia and inability to stand. The bird was first noted with dyspnea about three months prior to presentation and was severely dyspneic during the physical examination. A large mass could be palpated in the caudal abdomen. Necropsy revealed large cystic kidneys. Histologic changes in the right kidney (rk) were consistent with a renal adenocarcinoma, and the left kidney (lk) had undergone cystic changes.

Color 21.12

Articular gout in the elbow of a pigeon with renal failure (see Color 21.10).

Color 21.13

Polyuria can be caused by excitement, polydipsia, high-moisture diets (fruits) or renal disease. In this case, polyuria in a juvenile Blue and Gold Macaw occurred secondary to the excitement associated with handling.

Color 21.14

Hematuria is occasionally seen in birds. The blood can originate from the kidney and ureters, which is rare, or from the gastrointestinal tract or cloaca, which is common. In this African Grey Parrot, hematuria was occurring secondary to a bacterial nephritis.

Color 21.15

The presence of a large concentration of WBCs can cause urine to appear cloudy. In this cockatiel with severe metritis, both WBCs and RBCs were identified in the urine by cytology.

As an alternative to the cloacal cannula method, the fluid part of the excreta (urine) can be recovered immediately after excretion. The values for urine osmolality in excreted samples tend to be higher than those obtained from cloacal cannula samples. This might be explained by water resorption from the urine in the large intestine, which occurs under physiologic conditions⁴¹ but is prevented when using the cloacal cannula method. The cloacal cannula method would be expected to provide a better impression of the renal concentrating capacity of a patient.

A test for urine concentrating capacity of the racing pigeon has been developed as a model for differentiation of polyuric disorders in birds.¹ It was concluded that urine osmolality of 450 mOsmol/kg is indicative of the normal concentrating capacity of the kidneys. In polyuric birds without a diminished concentrating capacity, one day of water deprivation should be sufficient to cause a demonstrable rise in urine osmolality.

Because the specific gravity of urine has a positive correlation with the osmolality, it should be possible to determine specific gravity of avian urine with a refractometer. Further work is needed to establish the correlation between refractometric readings and osmometric values before refractometry can be recommended. Some practitioners believe that they can make an empirical prognostic determination based on the specific gravity of the urine in a patient.

Polyuria is confirmed by demonstrating hypotonic urine (osmolality, mOsmol/l or specific gravity).

Flow-osmol Factor

The flow-osmol factor can be defined as the product of the osmolality and urine volume per hour per kilogram. This value provides the limits within which the combination of both factors can be considered to be normal. There is a negative correlation between osmolality and urine flow. In this way, a low urine osmolality and a low urine flow, while both within their respective limits, should be considered abnormal when their combined value is below the normal values of the flow-osmol factor.

Nonprotein Nitrogen and pH

Uric acid concentrations, as mentioned in Table 21.1, are those that are found in supernatants of pigeon urine. The sediment has a much higher concentration of uric acid.

It is known that large quantities of cations are trapped in uric acid precipitates.^{32,33,44} The degree of cation trapping varies from 3-75% for Na⁺, 8-84% for

K⁺ and 17-32% for Ca⁺ and Mg⁺⁺. This should be considered when evaluating the values for these cations provided in Table 21.1. The Cl⁻ concentration in the urine mainly depends on the concentration of sodium chloride in the food.

Dietary protein does influence the total ammonia excreted but it has little effect on the urine ammonia concentration.³¹ Dehydration produces an increased ammonia concentration in urine, which is caused by the role of ammonia in regulating the acid-base balance.²⁰ Table 21.1 provides an indication of the pH range to be expected in the urine of granivorous birds. Determination of urine pH can be helpful in the diagnosis of acidosis in birds.^a

Protein

In healthy pigeons, protein concentrations in urine collected with the cloacal cannula method can be as high as 2 g/l. The excretion of mucoproteins and glycoproteins in the distal portion of the nephrons and the ureters is responsible for this low level proteinuria.³⁰ Severe, persistent proteinuria is a sign of increased glomerular permeability (eg, glomerulonephritis). Proteinuria is usually minimal or absent in diseases that primarily involve the tubules or interstitial tissue. Extreme protein loss through the kidneys can lead to severe hypoproteinemia.

Most urine dip-sticks are too insensitive to distinguish between moderate and severe proteinuria and may not properly detect proteinuria in polyuric patients. A false-positive protein result is common in psittacine birds that have had an alkaline urine. The use of the Ponceau S method¹⁶ for determination of urine protein concentration is recommended. With this method, protein is precipitated with trichloroacetic acid in the presence of the dye Ponceau S. The precipitate is then dissolved in sodium hydroxide, and the color intensity is measured spectrophotometrically at 545 nm.

Glucose

Glucose is normally absent from chicken urine,^{6,45} though small quantities (1.6 mmol/l) of monosaccharides have been described in ureteral urine samples collected from birds.⁴² The glucose concentrations mentioned in Table 21.1 are too low to be detected by rapid screening tests like Testape.^b

Polyuria and polydipsia accompanied by glucosuria do not always indicate diabetes mellitus. Diabetes mellitus can be diagnosed only if elevated plasma glucose concentrations have been demonstrated. In

mammals, Fanconi's syndrome is characterized by renal glucosuria, hyperaminoaciduria and hyperphosphaturia, as well as renal loss of potassium, bicarbonate, water and other substances conserved by the proximal tubule. Fanconi's syndrome should be considered as the final result of any one of many possible primary insults to proximal tubular function. The syndrome may be inherited or acquired. A case of renal glucosuria and proteinuria in an African Grey Parrot with severe renal damage was considered to be similar to the Faconi's syndrome. Glucosuria is frequently seen in psittacine hens with egg-related peritonitis. The problem is transitory if the peritonitis can be successfully managed.

Ketonuria

Ketonuria in mammals occurs when fatty acids are used instead of carbohydrates as the body's main energy source. It has been stated that ketonuria is a poor prognostic sign in birds, suggesting that catabolic processes lead to mobilization of fat and ketoacidosis.³⁹ This statement is probably incorrect for migratory birds. The primary energy source during migration is fat. In the premigratory state, the dry weight basis of some migratory birds is two-thirds fat. When this fat is used for energy during migration, it is broken down to fatty acids and glycerol. The body of migratory birds seems to have a metabolic system for preventing the accumulation of ketone bodies.¹² Diabetes mellitus has been mentioned as a cause of ketonuria in birds,^{11,38} however, in the author's opinion, the clinical importance of ketonuria needs further clarification.

Color

The color of urine varies but is generally white or off-white, pale yellow or light beige. Pigmented food items and medications may alter urinary color. B-complex vitamins can cause a yellow or brownish discoloration of the urine that can be misinterpreted as bilirubinuria (see Color 8). Berries in the diet can cause a blue-red discoloration of the urine (see Color 8). In liver diseases, biliverdinuria may result in a green-tinged urine (see Color 8).

Microscopic Examination of Urinary Sediment

Microscopic examination of urine sediment is diagnostic only when evaluating urine that contains relatively little uric acid. Furthermore, contamination of the urine with nonrenal components, such as feces or blood originating from the cloaca, must be considered. If performed properly, microscopic evaluation of the urine and protein determination are the most important methods for early detection of renal dis-

ease. Various cast types and cellular elements can be encountered in urinary sediment (Color 21.15). Cellular casts can contain epithelial cells, erythrocytes, leukocytes, bacteria and fungi. Granular casts are composed of degraded cellular components. Casts that have no cellular elements but have a yellow-orange color are suggestive of hemoglobin casts.³⁸ Eosinophilic tubular casts were suspected to contain myoglobin in an ostrich with acute muscle necrosis and toxic nephropathy.³⁷ Clinical experience suggests that the transition from cellular or granular casts to hemoglobin casts is a favorable prognostic sign and indicates resolution of the inflammatory process.³⁹

Microorganisms found in urine sediments are usually from fecal contamination; however, high bacterial counts in a relatively clean sample, together with urinary cast formation, is indicative of urinary tract infection. In male birds, sperm cells may be seen on routine microscopic examination of urinary sediment. Avian urine contains many amorphous urates, but other crystals may sometimes be noted.

Urinary Enzymes

Tissue enzyme profile studies in racing pigeons²² and budgerigars²⁶ have shown that renal tissues of these birds contain relatively high amounts of various enzymes. LDH, AST, CPK, AP, GLDH and ALT can be found in decreasing concentrations in renal tissue. From studies in dogs,¹⁸ it is known that the enzymes that are released during renal damage do not enter the systemic circulation but are voided with the urine. For this reason, determination of urinary enzyme activities could be of value for the diagnosis of renal cell damage, and the severity of cell damage might be judged by considering the site of origin of the various enzymes. For example, GLDH is known to be a mitochondrial enzyme and is expected to be released only after renal cell necrosis in which the cell organelles are damaged. In renal cell degeneration only the release of cytoplasmic enzymes is expected to occur. Further experimental studies in birds are needed.

Abnormal Urine Coloration

Hematuria is macroscopically visible when 0.1% of the urine contains blood (Color 21.14). Chemical test strips, like Hemastix,^e will show a positive reaction when 0.002-0.001% of the urine contains blood. The combination of microscopic examination of the sediment and the use of a test strip is more sensitive for the detection of hematuria than when either test is used alone. In mammals, hematuria is always pathologic. Red blood cells can originate all along the

urinary tract. In birds, hematuria is also possible when blood cells from the gastrointestinal and genital tract or cloaca are mixed with the urine sample. In carnivorous birds, the meat diet frequently results in a positive reaction. Both hematuria and hemoglobinuria can be demonstrated using test strips for hemoglobin. Hemoglobinuria will be seen when there is an increased erythrolysis.

Myoglobinuria can also cause a red coloration of urine, which cannot be distinguished from hemoglobinuria on routine chemical urinalysis. Myoglobinuria can be demonstrated spectrophotometrically. Exertional rhabdomyolysis is well known in a number of mammalian species (eg, man, horse, whippet, kangaroo) and has also been reported in flamingos^{9,10} and ostriches.³⁷ The resulting myoglobinuria can induce a severe toxic nephropathy.

Porphyrinuria is another cause of red coloration of the urine. In birds, the most common cause of porphyrinuria is lead poisoning. Amazon parrots with lead poisoning often produce a red or brown urine, which is assumed to be hemoglobinuria.³⁸ Lead is known to inhibit the activity of various enzymes involved in heme synthesis, which leads to porphyrinemia and porphyrinuria. Urine that contains high concentrations of porphyrins is wine-red in mammals. It is possible that the red or brown urine seen in Amazon parrots with lead poisoning is caused by porphyrins mixed with urates rather than hemoglobinuria. Porphyrins in urine will show a red fluorescence in ultraviolet light. When the test is negative, a blue fluorescence will be seen.

Radiology of the Urinary Tract

Survey radiographs provide information about the size, location and radiopacity of the kidneys. The paired kidneys are located in the ventral renal fossae of the synsacrum. The kidneys are surrounded by the abdominal air sacs, which extend as diverticuli between the kidneys and the pelvis. This finding explains why, at least in Psittaciformes, a rim of air can be seen dorsal to the kidneys. The loss of this dorsal rim of air is seen during pathologic swelling of the kidneys.²⁸ On a lateral radiograph, the kidneys appear as bean-shaped structures posterior to the last rib. The cranial part is more easily visualized radiographically because the caudal part is superimposed by the intestinal tract and pelvis. On a ventrodorsal radiograph, the kidneys are superimposed by the liver and the intestinal tract. Abnormalities that can be detected on survey radiographs include swelling

and crystalline inclusions indicative of urate deposits (Figure 21.3).¹⁹ Nephrocalcinosis or concrements in the kidney, ureters or cloaca can also be detected. Barium sulphate contrast of the gastrointestinal tract may be helpful in localizing intra-abdominal space-occupying lesions such as renal tumors. Occasionally, urate tophi of articular gout are visible on radiographs.⁸

Endoscopy and Biopsy

Endoscopy allows direct visualization of the complete urinary system (kidneys, ureters and cloaca). The endoscopic approach of choice is through a puncture site dorsal to the pubic bone and caudal to the ischium on the left side of the bird (see Chapter 13).²³ Although it is feasible to take renal biopsies in healthy birds,²³ there is considerable risk of fatal hemorrhage from this procedure, and it should always be performed with the appropriate equipment and ample experience.

In visceral gout, urate deposits can be seen on visceral organs, especially the pericardium and cranial border of the liver capsule (Color 21.7). A ventral midline approach just caudal to the sternum is preferred to endoscopically evaluate these structures.²³

Diseases of the Kidney^{2,7,13,14,35,37,40}

Infectious Diseases

Bacterial Infections

Bacterial infections of the kidney often occur secondary to septicemia but may also result from bacteria that ascend from the cloaca. *Staphylococcus*, *Streptococcus*, *Listeria*, *Escherichia coli*, *Klebsiella*, *Salmonella*, *Yersinia*, *Proteus*, *Citrobacter*, *Edwardsiella*, *Enterobacter*, *Morganella*, *Providencia*, *Serratia*, *Pasteurella* and *Mycobacterium* spp. have all been associated with nephritis. Diagnostically, WBC evaluation, total protein and protein electrophoresis provide useful information on the systemic inflammatory reaction. Bacterial cultures of blood and urine may reveal the causative organism. Mycobacterial infections often cause monocytosis that can be demonstrated on a peripheral blood smear.

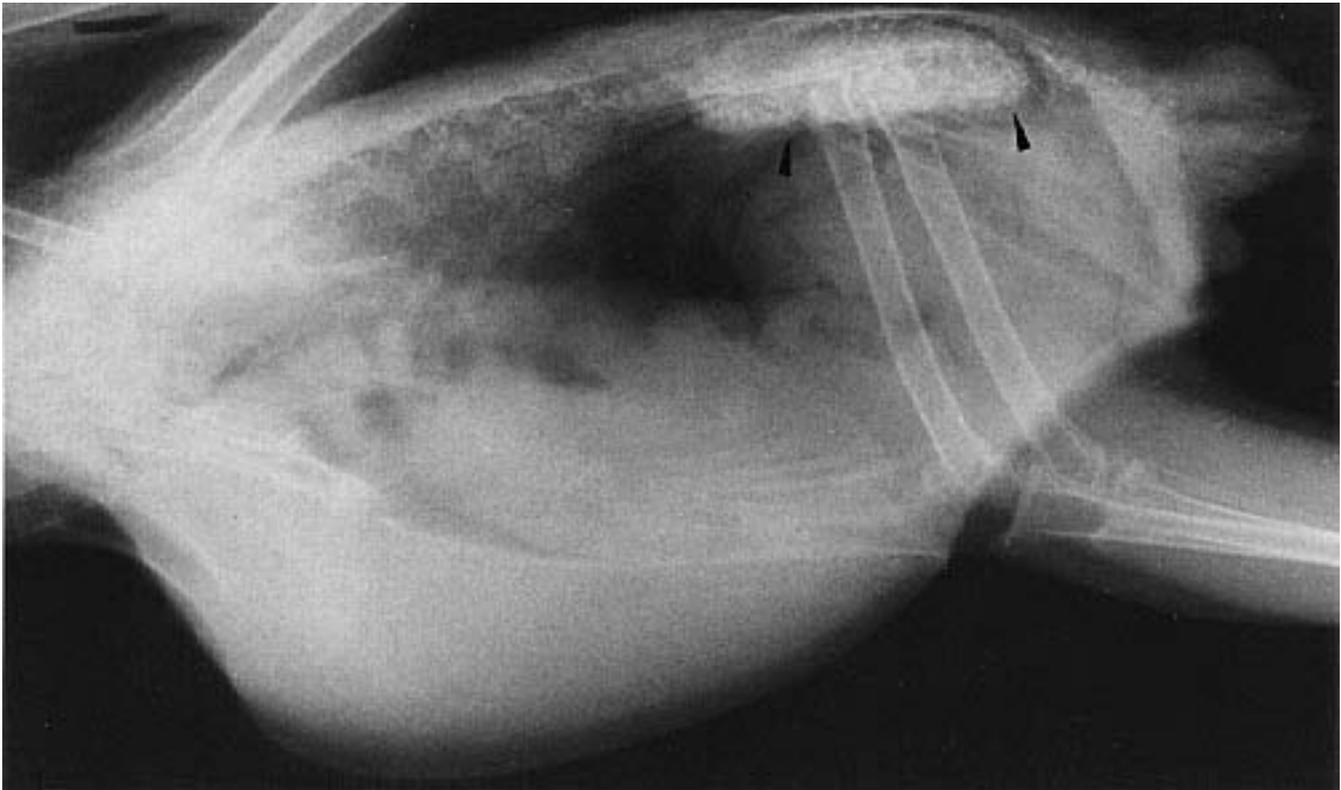


FIG 21.3 An African Grey Parrot of unknown age was presented for a pre-purchase examination two years after being imported into the country. A CBC and avian profile were unremarkable. Radiographs indicated nephrocalcinosis (arrows). This is considered an abnormal finding that occurs frequently in African Grey Parrots. Nephrocalcinosis has been associated with hypervitaminosis D.³⁷

Viral Infections

Viral infections are usually multisystemic, although some viruses like avian polyomavirus and infectious bronchitis virus in chickens demonstrate a tropism for the kidney. Other viruses that have been associated with renal lesions include Newcastle disease virus, paramyxovirus of pigeons, reoviruses, viruses belonging to the leukosis/sarcoma group and herpesviruses (eg, Pacheco's disease virus and pigeon herpesvirus).

Mycotic Infections

Renal infarction as a complication of mycelium invasion of blood vessels secondary to pulmonary mycotic disease is common. Abdominal air sac aspergillosis with renal involvement *per continuitatem* has also been reported (Color 21.2). In the latter case, ischiatic nerve involvement resulted in unilateral paralysis.

Parasitic Infections

Granulomatous nephritis due to *Isospora*, *Cryptosporidium*, *Microsporidium* and *Encephalitozoon* spp. has been reported in a variety of avian species.

Eimeria truncata is a well known cause of renal coccidiosis in geese. Adult trematodes of *Tanaisia bragai* can be found in collecting ducts of chickens, turkeys and pigeons.

Noninfectious Diseases

Congenital Defects

Agnesis and hypoplasia of part of the kidneys have been described in birds. Compensatory hypertrophy of the intact poles is common (Figure 21.4). Renal cysts have also been described and may be congenital in origin (Color 21.11). Diagnosis can be made with urography and laparoscopy.

Metabolic Disorders

Hypervitaminosis D and elevated dietary calcium can both cause hypercalcemia and lead to deposition of calcium salts in the renal parenchyma (nephrocalcinosis). Calcinosis of other organs may also be noted. This condition can be detected radiographically, and the history may indicate oversupplementation of calcium or vitamin D in the diet. Nephrocalcinosis should not be confused with urolithiasis. The latter



FIG 21.4 An African Grey Parrot with agenesis of the cranial and middle divisions of the right kidney. Visualization of the kidneys is enhanced by the presence of calcium phosphate crystals. Pneumonia and consolidation of the left air sacs (arrows) are also present (courtesy of Marjorie McMillan).

condition is the most prevalent renal disorder of laying hens. Suggested causes include excess dietary calcium, low phosphorous and infectious bronchitis virus. Unilateral or bilateral ureteral concretions of calcium urate can lead to postrenal renal failure. A diagnosis may be possible with cloacal palpation, radiography, excretory urography and endoscopy.

Hypovitaminosis A can cause metaplasia of the epithelium of the ureters and collecting ducts and decreased secretions of mucus in these structures. This may lead to precipitation of urates and ureteral impaction.

Amyloidosis

Renal amyloidosis often occurs in Anseriformes in conjunction with amyloidosis of other organs (eg, liver) secondary to chronic inflammation. There is a deposition of amyloid A, a degraded fragment of an acute phase reactant. In ducks, renal amyloidosis can lead to massive proteinuria and nephrotic syndrome due to severe glomerular damage. Clinically, this may be recognized as ascites, or edema of the feet and legs.

Toxic Nephropathies

Many nephrotoxins cause renal tubular necrosis including aminoglycosides, heavy metals, and mycotoxins such as aflatoxin (*A. flavus* and *A. parasiticus*), ochratoxin (*A. ochraceus* and *Penicillium viridicatum*), oosporein (*Chaetomium trilaterale*) and citrinin (*P. citrinum*).

Salt (NaCl) poisoning has been documented in various species. Salt poisoning via drinking water can lead to right ventricular failure and ascites. Salt poisoning via food leads to acute renal failure with urate impaction of the ureters. Clinical signs include polydipsia and polyuria, or anuria if urate impaction of the ureters occurs. The principal toxic effect is an imbalance in sodium and potassium homeostasis. Right ventricular failure should be suspected with ascites and can be diagnosed by ECG (see Chapters 27 and 37).

Neoplasia

Budgerigars have a high incidence of primary renal tumors, especially adenocarcinoma and nephroblastoma (younger birds) (Color 21.11). A viral origin has been suggested.³⁵ The kidney is a potential metastatic site for tumors of nonrenal origin, especially lymphoproliferative diseases (leukosis). Unilateral or bilateral paralysis caused by compression of the ischiatic nerve is a common clinical sign associated with renal malignancies in birds (Color 21.4). Abdominal enlargement is common when a renal mass causes caudoventral displacement of the ventriculus or ascites. A renal tumor may be radiographically detectable with or without the use of barium sulphate to differentiate the margins of the gastrointestinal tract.

Ureteral Obstruction

Displacement or obstruction of ureteral orifices can occur due to intestinal or cloacal prolapse or cloacal obstruction caused by fecaliths, uroliths, foreign bodies, tumors or inflammatory processes. A bilateral obstruction will rapidly lead to visceral gout. Unilateral obstructions will lead to atrophy and compensatory hypertrophy of the contralateral kidney.

Renal Hemorrhage

Renal hemorrhage can be caused iatrogenically during endoscopy if improper technique is used. Sporadic renal hemorrhage in male turkeys and Psittaciformes has been documented with extravasated blood remaining confined under the renal capsule or retroperitoneally (Color 21.5). It can also occur as a complication of renal pathology (eg, tumor). Peracute mortality is common.

Therapeutic Considerations

Prerenal Renal Failure

Treatment of prerenal renal failure caused by dehydration or shock is usually successful; however, the challenge is diagnosing and treating the initial cause of dehydration. Rapidly expanding the circulatory volume with intravenous fluids will usually restore normal renal function within hours (see Chapter 15).

Postrenal Renal Failure

The treatment of postrenal renal failure caused by urolithiasis requires removal of the uroliths. This is a substantial surgical challenge. Successful extracorporeal shock wave lithotripsy for removal of uric acid concretions in the urinary tract has been reported in a Magellanic Penguin and may be attempted in other affected birds.²⁷

Acute Renal Failure

Once a diagnosis of acute (reversible) renal failure is made, immediate and aggressive therapy is indicated to prevent further damage. Suggested therapy for managing uric acid nephropathy in mammals provides some insight into the treatment of birds with a similar condition but different etiology. Acute oliguric renal failure associated with hyperuricemia and marked hyperuricaciduria in man occurs sporadically due to the precipitation of uric acid crystals in the distal parts of the renal tubules, the collecting ducts, the renal pelvis or the ureters.

This condition most frequently occurs secondary to the administration of cytotoxic drugs or irradiation, whereby the dissolution of a neoplastic mass liberates a heavy load of nucleic acid that must be catabolized and excreted by the kidneys. The uric acid excretion rises suddenly, uric acid precipitates in renal tubules and acute oliguric renal failure ensues. Contributing factors include excretion of an acid urine secondary to metabolic acidosis, dehydration and the use of uricosuric drugs (adrenocorticosteroids). Plasma uric acid concentrations may be as high as 4770 $\mu\text{mol/l}$ (80 mg/dl). Treatment includes maintaining a high alkaline urine flow by infusing mannitol 20% (1000 mg/kg) every 15-20 min and sodium bicarbonate supplemented with intravenous fu-

roseamide. The prognosis for recovery of renal function is good if diuresis can be achieved.⁴⁶

Successful treatment of a Red-tailed Hawk with acute obstructive nephropathy that was induced by administration of allopurinol has been reported.²⁴ The bird showed signs of depression 18 hours after the third dose of allopurinol was given. Plasma chemistry revealed hyperuricemia (uric acid 5,721.6 $\mu\text{mol/l}$). A diagnosis of renal tubular nephrosis caused by oxypurinol, xanthine or uric acid deposits in the tubuli was made. Intravenous and subcutaneous saline, corticosteroids and furosemide (1 mg/kg) were administered twice daily in an attempt to restore renal function. Urine production was restored and, after 24 hours, plasma uric acid concentration had decreased to 3,814 $\mu\text{mol/l}$. Fluid therapy, corticosteroids and diuretics were continued. Plasma uric acid had decreased to 1,639 $\mu\text{mol/l}$ 72 hours later. The bird fully recovered after two weeks of intensive treatment with intravenous fluids and supportive alimentation. Although corticosteroids were used in this case, these drugs have been shown to be uricosuric in man and should be considered contraindicated in most cases of renal failure.

In anuric/oliguric renal failure, fluid intake in the patient should be restricted to fluid loss (renal loss, loss from the gastrointestinal tract and insensible loss of about 20 ml/kg/day). Assessment of fluid requirements can be based on this general outline but must be monitored by daily weight determination and observation for clinical signs that would indicate overhydration or dehydration. In patients that are anorectic and not receiving assisted feedings, some allowance should be made to account for tissue catabolism. Losses of 2.5% body weight per day are possible in totally anorectic parrots. Sodium, potassium and protein intake should be discontinued and calories should be given in the form of fat and carbohydrates. Alternatively, a low-protein diet containing all essential amino acids can be given. Furosemide should be used in an attempt to restore or increase urine flow and potassium excretion.

In the polyuric phase that follows the anuric phase, fluid and electrolyte balance should be carefully monitored to prevent dehydration, hyponatremia and hypokalemia. Intravenous and subcutaneous infusions with lactated Ringer's solution should be continued on a daily basis. Because bacteria are often incriminated as the cause of renal failure, use of non-nephrotoxic bactericidal antibiotics that are effective against the most commonly encountered bac-

teria are indicated. A combination of piperacillin and claforan has been suggested, although these drugs have a similar mode of action.³⁹ Vitamin A supplementation is always indicated in hyperuricemia, because hypovitaminosis A is a common cause of renal failure.

Effects of Drugs

Allopurinol

A recent study²⁴ has demonstrated that oral administration of allopurinol does not prevent the occurrence of physiologic postprandial hyperuricemia in Red-tailed Hawks. Contrary to expected findings, administration of allopurinol caused a severe hyperuricemia and induced gout in three out of six, clinically normal Red-tailed Hawks. This drug is known to reduce plasma uric acid concentration in man with hyperuricemia. The results of this study seem to indicate that allopurinol is contraindicated for the treatment of hyperuricemia in Red-tailed Hawks. Previous reports discussing effective therapy in parrots with allopurinol may have been coincidental³⁶ and related to physiologic variations in plasma UA concentrations in relation to food intake. Further work is needed in carnivorous and granivorous birds to establish fasting and postprandial reference intervals of plasma UA concentrations and the possible effects of allopurinol in birds. Recommendations for therapy based on single observations in individual birds must be cautiously applied to the management of any avian disease (including gout) until research can determine that a therapy is safe.

The extreme renal tubular nephrosis observed following allopurinol administration in Red-tailed Hawks²⁴ might be explained by the formation of oxypurinol, the relatively insoluble and nephrotoxic end-product of allopurinol. Alternatively, renal damage might have been caused by the deposition of xanthine crystals. Xanthine and hypoxanthine are precursors of uric acid, and concentrations of these substances increase when the xanthine oxidase inhibitor, allopurinol, is administered. High-pressure liquid chromatography is necessary to determine which metabolic product is being deposited in the tubules. Histologic techniques are not sufficient to determine the character of the deposits in the tubules, because they are generally washed away during preparation of the tissues for sectioning.

Corticosteroids

Corticosteroids are known to be uricosuric in man⁴⁶ and may be contraindicated in avian hyperuricemic

conditions. Prednisolone has been used in budgerigars with renal tumors. The author states that although she does not know whether the prednisolone prolongs life, it may improve the quality of life by diminishing the pressure on the ischiatic nerve and stimulating appetite.²

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Products Mentioned in the Text

- a. Clinistix, Miles Diagnostics, Elkhart, IN
- b. Testape, Eli-Lily Benelux NV, Amsterdam
- c. Hemastix, Miles Diagnostics, Elkhart, IN