54
GOUT

DOUGLAS R. MADER

Gout, in any of its forms—visceral, articular, and periarticular—is a common affliction in reptilian patients. Hippocrates, 2500 years ago, wrote of gout as a disease of the big toe, hand, or knee of man and called it Podagra, Cheigagra, or Gonagra, respectively, depending on the joint affected. Little new was added to the description of gout until the late seventeenth century when Anton van Leeuwenhoek described the crystals that we now routinely associate with gouty tophi. Over the last three decades, gout, and other crystal-related joint diseases (e.g., pseudogout), has been thoroughly elucidated in human medicine.

Although gout is frequently seen in humans and primates, it is not a common problem in general veterinary medicine. Other than in the Dalmatian dog, gout is not a topic of much discussion in the veterinary literature.[1] As a result, exotic animal veterinarians, especially those who specialize in avian and reptilian patients, must rely on the human medical literature for information regarding the diagnosis and treatment of this disease.[2-8]

Few studies have been reported that cite the incidence of gout in reptile patients. Kolle and Hoffman[9] reported a retrospective analysis of 280 European Tortoise carcasses that showed an incidence rate of 64.3% of all necropsies had evidence of renal disease. Of those, 16% showed signs typical of gout with tophi in the kidneys.[9]

CAUSES

All reptiles need protein in their diets. Not all protein is the same. For example, there are animal source proteins (meat) and plant source proteins (vegetables). Carnivores, such as snakes and monitor lizards (*Varanus* spp.), need animal source proteins in their diet, whereas vegetarians, such as the Green Iguana *(Iguana iguana)*, must have plant source protein in their diet (Figure 54-1). Each type of animal is physiologically adapted to efficiently use a specific type of dietary protein.

Although carnivores can eat plant source proteins, the diet is not complete and they eventually have certain amino acid deficiencies. In comparison, vegetarians can eat animal source proteins, but the differences in the amino acids may overwhelm the animal's ability to efficiently process the nutrients and may lead to serious side effects.

Nucleic acids in the diet are degraded by nucleases to nucleotides (Figure 54-2). These nucleotides undergo further enzymatic hydrolysis to yield free purine and pyrimidine bases. Additional purine and pyrimidine bases are synthesized in the liver from amino acids. If these free bases are not reused by the body, they are further degraded and ultimately excreted. The pyrimidines are catabolized to the end products CO_2 and NH_3.

In some vertebrates, including man, nonhuman primates, the Dalmatian dog, birds, and some reptiles, the end product of purine degradation is uric acid (Figure 54-3).[10] In the remaining mammals and reptiles, the end product is allantoin. In the fishes, the allantoin is further broken down into allantoic acid and urea.

In aquatic invertebrates, the end product of purine metabolism is ammonia. One other notable exception occurs in the pig and the spider where the excretory end product of purine degradation is guanine.[10]

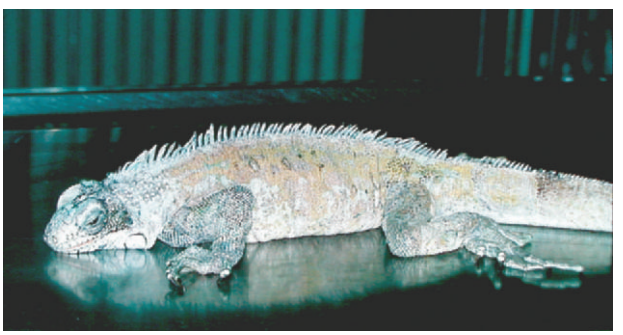

FIGURE 54-1 This gouty Green Iguana *(Iguana iguana)* was fed a diet that consisted mainly of cat food for its entire life. Note the poor condition of the scales, the swollen eyes, and the knobby curled digits.

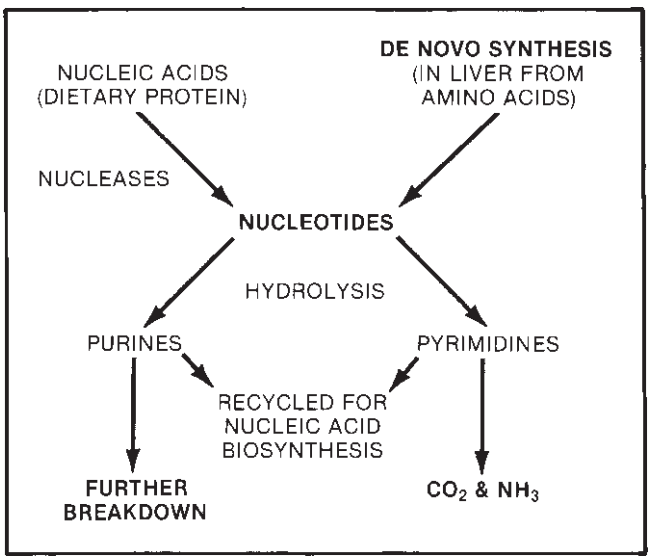

FIGURE 54-2 Nucleic acid breakdown and nucleotide formation.

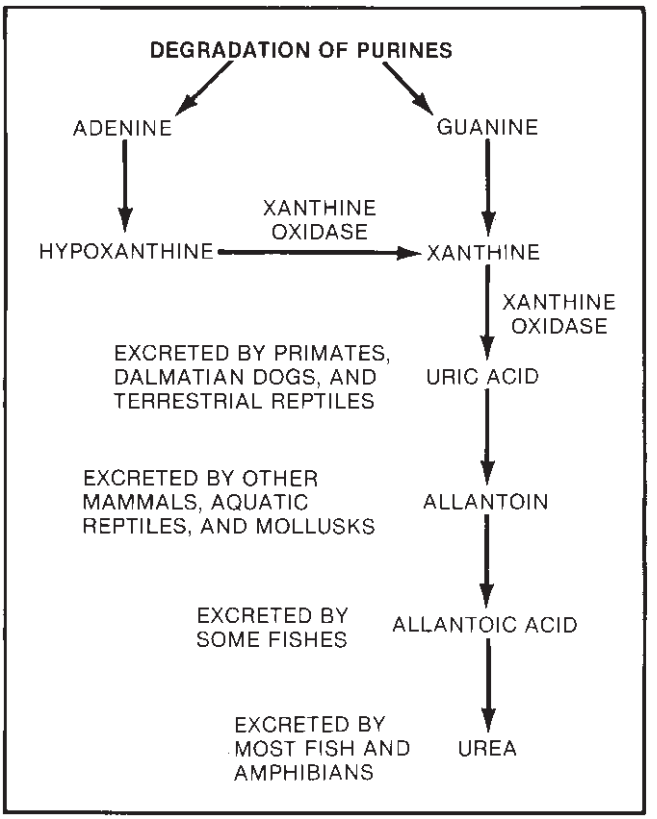

FIGURE 54-3 Degradation of purines.

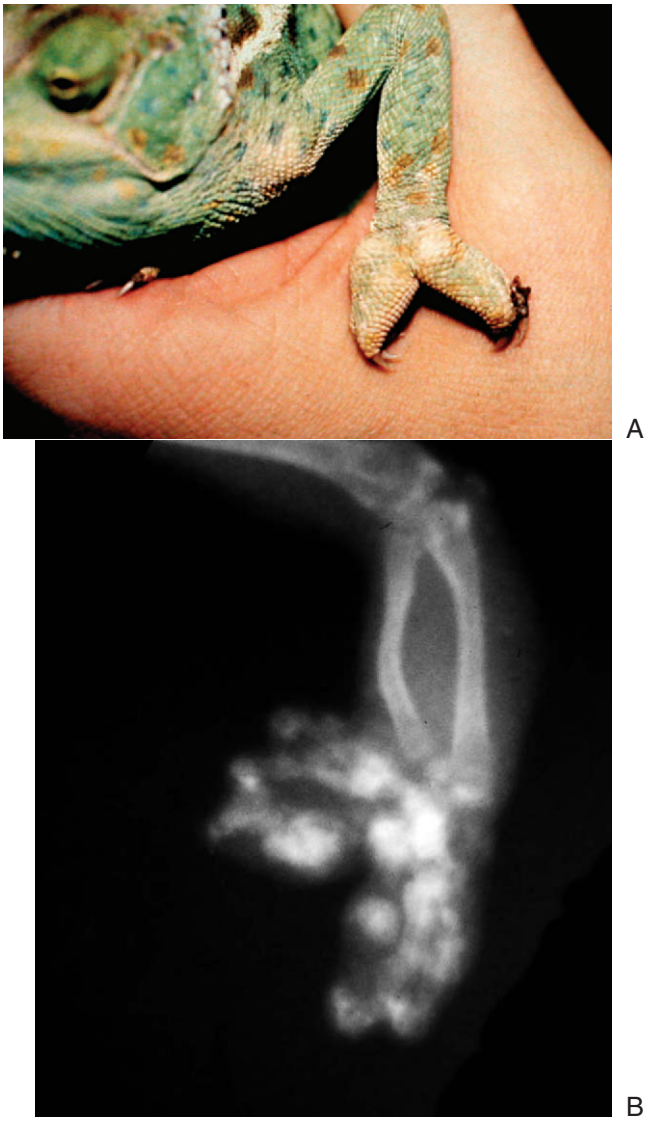

FIGURE 54-4 **A,** Veiled Chameleon *(Chamaeleo calyptratus)* with whitish-yellow nodules around and over the carpal joints. This patient had difficulty ambulating or grasping with its digits. **B,** Radiograph of the carpal joint. Note the gout-induced lytic damage to the bones.

In humans, the formation of uric acid from the degradation of purines has been extensively studied. Degradation of the major purines, adenine and guanine, starts initially with a conversion to hypoxanthine and then to xanthine for adenine and directly to xanthine for guanine. Both of these pathways require the flavoprotein, xanthine oxidase, to form uric acid (see Figure 54-3).[10]

In vertebrates, this uric acid is derived from both exogenous and endogenous nucleic acids. In man, approximately 0.5 gram of uric acid is excreted daily, even though as much as 5 grams of free purines are formed during the same period.[11]

In reptiles, uric acid is cleared from the blood through the kidney tubules, unlike in mammals, where urea is excreted primarily with filtration. Urates are poorly water soluble and precipitate at low concentrations. In alligators, studies have shown that dehydration does not impair uric acid excretion, but lower ambient temperature does decrease renal tubule function.[12] Dantzler,[13] however, reports that the nephron actively secretes three times more urates when normally hydrated. In the bird, uric acid excretion is regulated with plasma uric acid concentration and renal portal blood flow.[14]

In the blood, uric acid is present predominantly as monosodium urate. Both the free uric acid and the urate salts are relatively insoluble in water. When the concentration of either or both of these forms becomes elevated in the blood (a condition called hyperuricemia) or in other body fluids, such as synovial fluid, the uric acid crystallizes, forming insoluble precipitates that are deposited in various tissues throughout the body.

Crystallization that occurs in the synovial fluid results in an acute painful inflammation of the joint, a condition called gouty arthritis (Figure 54-4). Crystals can also deposit around the joints (periarticular gout) (Figure 54-5) and in other subcutaneous and internal tissues (visceral gout) (Figure 54-6). The uric acid crystals form small white nodules, called tophi, that are clearly visible to the unaided eye.

True gout is caused by the presence of monosodium urate crystals. Pseudogout, which occurs as a result of any crystal other than sodium urate, also causes an acute inflammatory response in the joint affected. Wenker et al[15] reported a case of pseudogout caused by calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) in two Red-bellied Short-necked Turtles *(Emydura albertisii).*

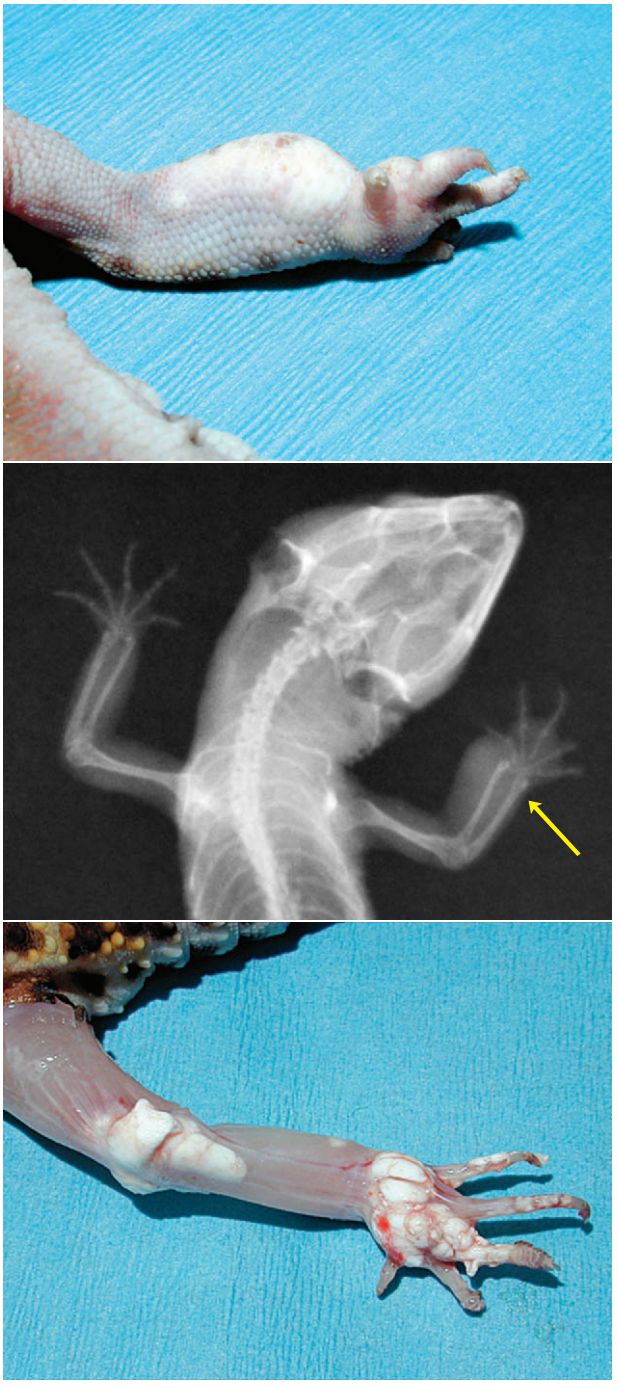

FIGURE 54-5 **A,** Periarticular gout in a gecko. Note the whitish nodules around and over the carpal joints. **B,** Radiograph of the carpal joint. Note the joint itself does not appear to be damaged. **C,** Prosection of the patient in **A** and **B**. Note the periarticular accumulation of tophi around the elbow, carpus, and phalanges. *(Photographs courtesy S. Barten.)*

TYPES

The two classifications of gout are primary and secondary. In primary gout, the hyperuricemia is the result of an overproduction of uric acid. Approximately 95% of the humans affected with gout have the primary form, which is believed to be familial and possibly related to inherited enzyme defects.

Secondary gout occurs when the hyperuricemia results from an acquired chronic disease or a drug that interferes with the normal balance between the production and excretion of uric acid. Diuretics are the drugs most implicated in causing gout. Furosemide, a diuretic frequently used in veterinary medicine, decreases the renal tubular excretion of urates and is contraindicated in dehydration, hyperuricemia, or cases of suspected gout.

Examples of chronic diseases that affect uric acid excretion include renal disease, hypertension, and starvation. Hyperuricemia can also be caused by myeloproliferative disorders (accelerated metabolic processes) and hemolytic disorders (increase in cellular breakdown).

In humans, hyperuricemia is associated with obesity and drug, alcohol, and protein (purine) consumption, which suggests that environmental factors and genetic factors contribute to the development of gout. In reptile medicine, the environmental factors are the most commonly implicated.

Three stages of gout are described in humans. The first is an asymptomatic hyperuricemia. In this stage, tophi, renal stones, and arthritic symptoms are not present. A person may remain asymptomatically hyperuricemic throughout life.

In the second stage, which is an acute gouty arthritis, the symptoms can occur abruptly, with the most common symptom being pain. Arthritic attacks may subside without treatment. On recovery, all symptoms resolve completely. Subsequent attacks may or may not occur. The "intercritical period" between attacks can be days to years.

The third stage is called tophaceous gout. A progressive inability to excrete uric acid results in urate crystal deposits (tophi) in cartilage, synovial membranes, tendons, and soft tissue. Each tophus consists of a complex of urate crystals surrounded by a granuloma. This granuloma consists of macrophages that have developed into epithelial and giant cells. These tophi produce irregular swellings around joints.

In reptilian patients, common sites for tophi deposition include the pericardial sac, kidneys, liver, spleen, lungs, subcutaneous tissue, and other areas of soft tissue.

In humans, renal calculi occur with increasing levels of serum urates. The stones can range in color from pale yellow to reddish brown. Some of the stones consist of 100% monosodium urate, which are radiolucent, and others, which are complexed with calcium oxalate or calcium phosphate, are radiopaque. Cystic, not renal, calculi are a common finding in reptilian patients. However, renal tophi are a common finding in patients with visceral gout (Figure 54-7).

In reptile medicine, various risk factors contribute to the development of gout, such as dehydration, kidney damage (especially tubular disease), and excessive intake of purine-rich meals. This latter condition is common in herbivorous animals fed a diet high in animal protein (e.g., Green Iguanas fed a diet of cat food).[16]

Misuse of potentially nephrotoxic antibiotics, such as the aminoglycosides and the sulfonamides, can cause tubular nephrosis and predispose the patient to hyperuricemia. This is a common sequela in patients being treated, but the state of hydration is ignored (Figure 54-8).

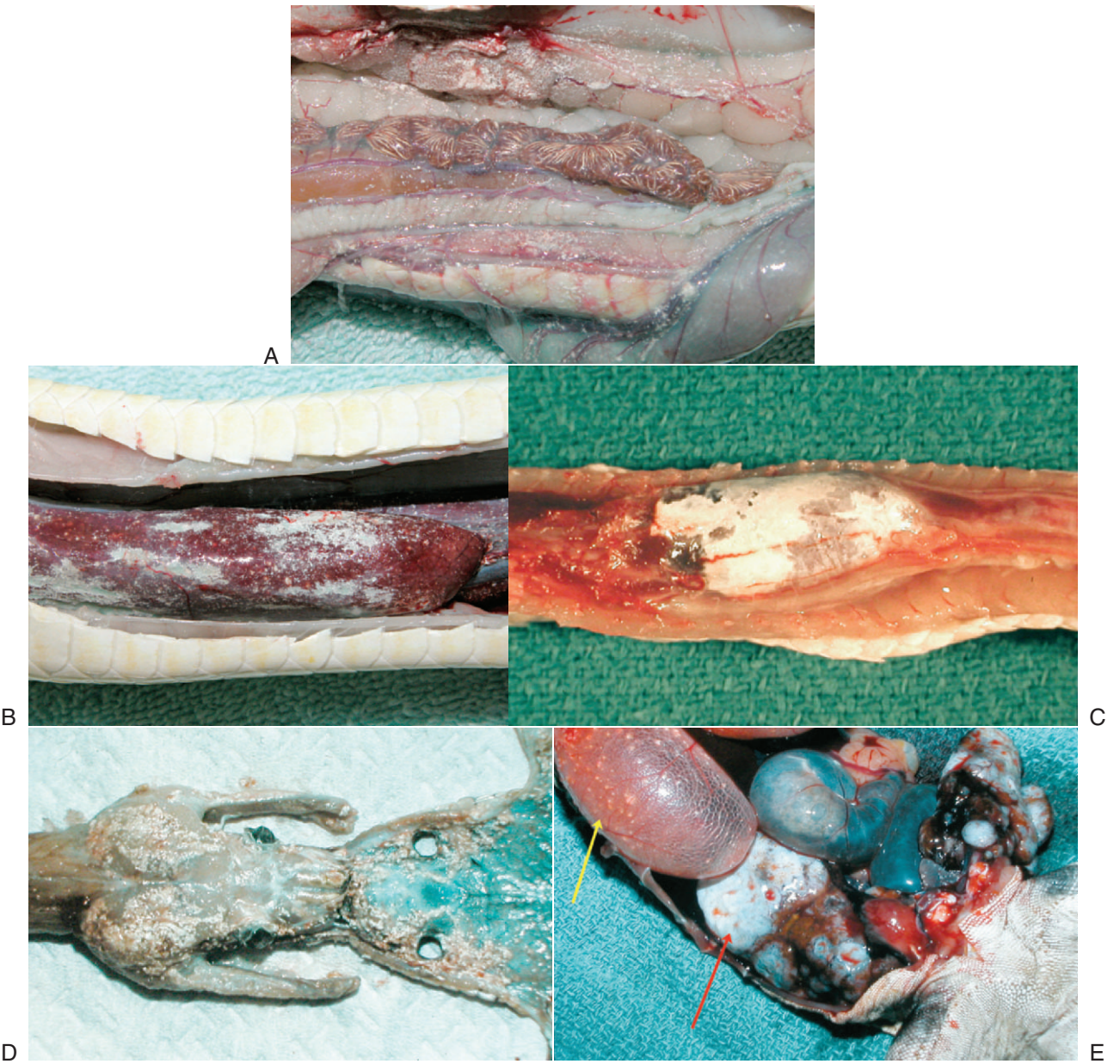

FIGURE 54-6 In reptilian patients, common sites for tophi deposition include **A,** the kidneys (note the powdery tophi crystals scattered throughout the membranes); **B,** the liver; **C,** the pericardial sac; **D,** the muscles of the head and subcutaneous tissue; and **E,** the lungs *(yellow arrow)* and fat pads *(red arrow)*.

DIAGNOSIS

Diagnosis of gout, either articular or visceral, is made on the basis of history and clinical examination. Diet, availability of water, ambient temperature, and humidity all play important roles in development of the disease. Laboratory sampling may or may not show hyperuricemia, depending on the state of health at the time of sampling. Blood urea nitrogen and creatinine are usually of little value in interpretation of renal disease in reptilian species.

Radiographs may reveal lytic lesions in, around, or near the joints. If renal or cystic calculi are composed of monosodium urate stones, they may go unnoticed; but if the calculi are complexed with calcium, the stones are readily apparent.

A definitive diagnosis of gout is made on demonstration of monosodium urate crystals in the joints of affected patients or within tophi of diseased tissue (Figure 54-9). A polarizing filter makes identification of the biorefringent crystals easier.[16,17]

TREATMENT

Treatment of gout in human medicine is threefold: lower the serum uric acid level with antihyperuricemic drugs such as

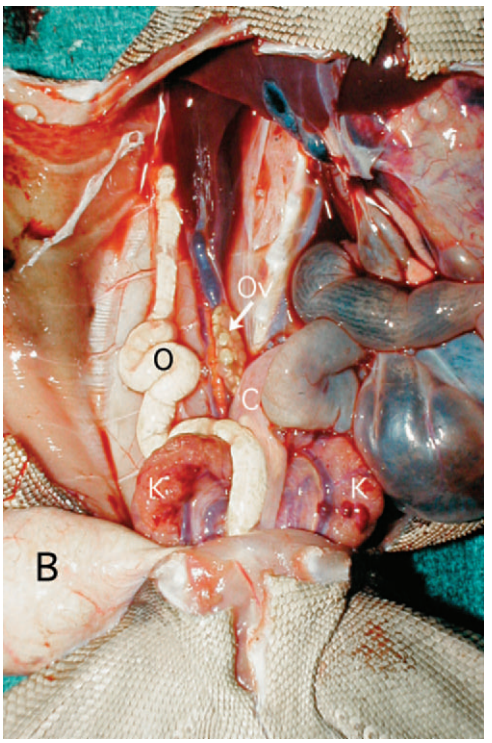

FIGURE 54-7 A Green Iguana *(Iguana iguana)* with severe renomegaly from gout. The kidneys were so enlarged that the pelvis was almost completely obstructed. As a result, urate-laden urine retrofluxed back into the animal's right oviduct. *O,* Oviduct; *Ov,* ovary; *C,* colon; *K,* kidney; *B,* bladder.

FIGURE 54-8 This python was treated with an aminoglycoside for infectious stomatitis. The veterinarian noticed the whitish lesions in the gingiva. Thinking it was a progression of the infectious stomatitis, he increased the dose. In actuality, the lesions were not infectious in origin but were depositions of gouty tophi. The snake died of extensive visceral gout.

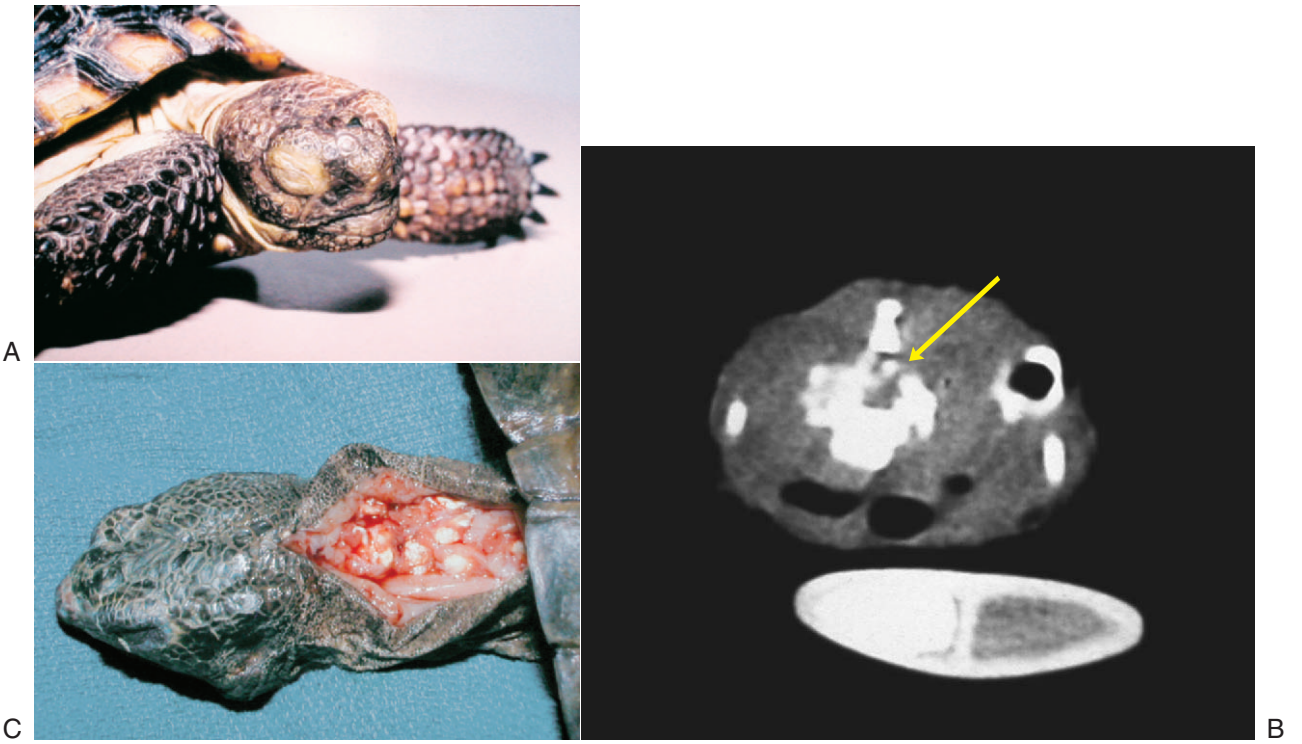

FIGURE 54-9 **A,** This tortoise presented with a right-sided head tilt. **B,** The computed tomographic cross section through the neck of this patient shows a small area of bone destruction caused by uric acid crystals *(yellow arrow).* **C,** The patient was euthanized, and necropsy was performed. The numerous whitish crystals along the dorsal cervical region were all gouty tophi.

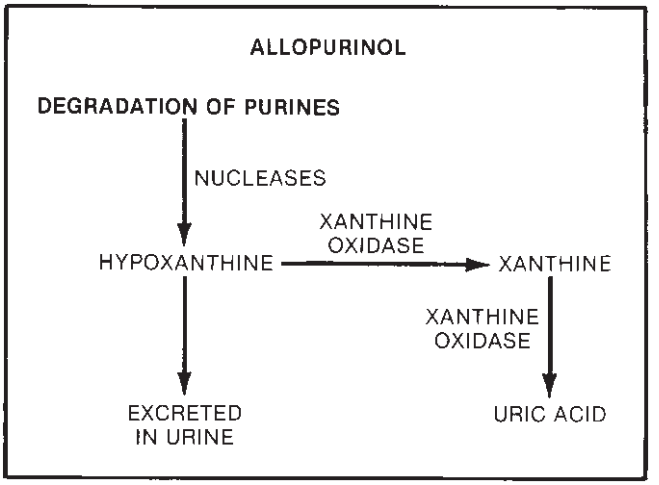

FIGURE 54-10 Allopurinol decreases uric acid production by inhibiting the actions of xanthine oxidase.

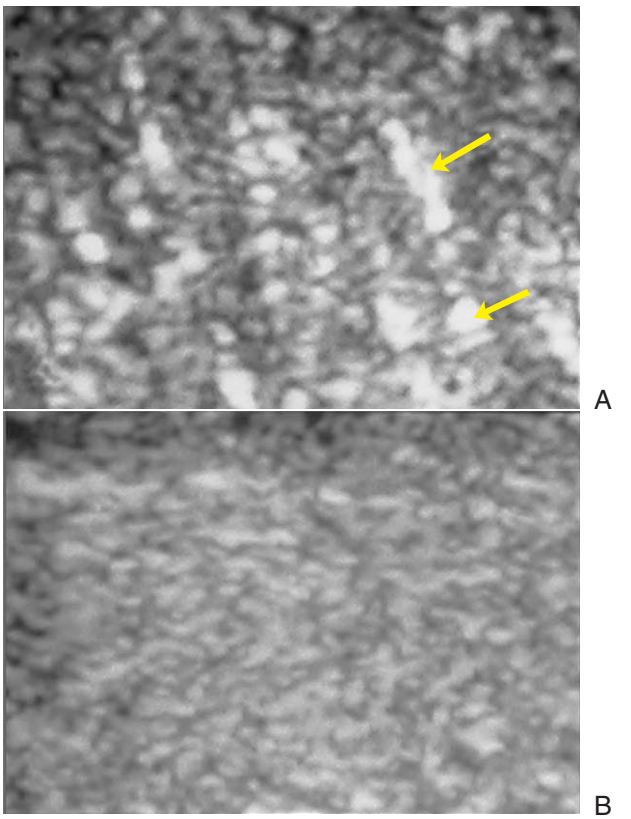

FIGURE 54-11 **A,** Renal ultrasound from a European Tortoise with severe renal gout. The tophi, which are scattered throughout the renal parynchema, are hyperechoic *(yellow arrows)*. **B,** The same patient as in **A**. Note the homogenous-appearing renal parynchema and the absence of hyperechoic tophi. The tophi dissolved after 2 to 4 months of treatment with 50 mg/kg allopurinol, given every third day. *(Photographs courtesy P. Kolle.)*

allopurinol (Figure 54-10), promote urate excretion with uricosuric drugs such as probenecid, and manage acute gouty arthritis attacks with antiinflammatory drugs such as colchicine and corticosteroids. In humans, the goal of therapy is to keep the serum uric acid levels less than 6 mg/dL. Doing so is believed to prevent future attacks and to dissolve existing tophi.

In theory, the treatment goals for reptiles with gout are similar to those in humans. However, little research has been done surrounding the treatment of gout in reptiles. Recent reports suggest that allopurinol therapy is effective in reptiles (Figure 54-11),[18] with results consistent with goals in human medicine.[19,20]

Many different dosages have been reported in the recent herpetologic literature (Table 54-1). Most dosages used, however, are based on extrapolations from the human dosages (Table 54-2). These drugs are not without side effects, and the clients should be warned when they are used in reptile patients.

If the patient has severe gouty arthritis, surgically entering the affected joint and physically removing the uric acid crystals is possible. However, by the time the crystals have formed, severe joint damage is usually present. Between this damage and the surgical damage done to the joint, even by the best of surgeons, the joint is usually permanently affected. In these cases, treatment may be best attempted with long-term allopurinol therapy.

CONCLUSION

All this points to the fact that gout is a serious problem in reptiles. Because of their primitive physiology and unique, often poorly understood nutritional requirements, they are more prone to this disease. Although we still have a great deal to learn about gout in reptiles, we do know that in most instances it is usually preventable.

Proper diet, correct ambient temperatures, and continuous access to fresh clean water all thwart the development of gout. In addition, the proper use of medications, especially antibiotics, can ensure against kidney damage and secondary gout formation.

The overall prognosis for patients with severe gout is poor. Advanced cases can be maintained for a short period. Keep in mind, on the basis of our knowledge in human medicine, that acute gouty attacks are painful, and although how reptiles interpret pain is not known for sure, one can only assume that they feel the same discomfort as their human counterparts. As such, patients with gout should be given proper medications to alleviate any pain and suffering that they might experience.

More research needs to be done on reptilian patients with gouty symptoms. Newer drugs are available on the human market that show promise and have potential for use in herpetologic medicine. Xanthine oxidase inhibitors such as oxipurinol and febuxostat are first-line treatments for human patients with renal calculi, renal insufficiency, and hyperuricemia. These are safe and well tolerated with few side effects.[21]

Recombinant urate oxidase is used for the treatment of tumor lysis hyperuricemia in human cancer patients.

Table 54-1 Dosages of Allopurinol Reported in Clinical Reptile Cases

Dose	Frequency	Duration	Comment	no.	Reference
50 mg/kg	q 24 h	30 d	A	73	18
Followed by:					
50 mg/kg	q 72 h	3 y	B		
9.93 mg/kg	q 24 h	30 d	C	1	19
Followed by:					
3.31 mg/g	q 24 h	90 d			
20 mg/kg	q 24 h	90 d	D	1	20
At 21 days into therapy, the following was added:					
Probenecid (250 mg)	q 12 h	45 d	E	1	

All doses were administered orally.
A, 97.3% of all tortoises showed decrease in [uric acid] by day 7. *B*, Uric acid tophi in kidneys disappeared 2 to 4 months after [uric acid] < 2 mg/dL. *C*, Joint inflammation disappeared after 5 months of treatment; all clinical signs gone by 7 months later. *D*, [Uric acid] returned to normal (8 mg/dL) after 75 d of allopurinol, 52 days after the start of probenecid. *E*, The tortoise had a relapse and died 30 days later, despite reinstatement of treatment.

Table 54-2 Medications Commonly Used for the Treatment of Gout in Humans

Drug	Dose	Comments
Allopurinol	20 mg/kg, PO, q 24 h	Decreases production of uric acid (blocks xanthine oxidase)
Probenecid	250 mg, PO, bid (increase as needed)	Blocks resorption of uric acid by kidney tubules, increasing uric acid excretion
Sulfinpyrazone	100-200 mg, PO, bid (increase as needed)	Blocks resorption of uric acid by kidney tubules, increasing uric acid excretion
Colchicine	0.5-1.2 mg, PO q 2 h; or 2 mg loading dose IV, followed by 0.5 mg IV q 6 h	Reduces inflammatory response to monosodium urate crystals in joint tissues; positive response usually seen within 24 h

PO, Orally; *q*, every; *bid*, twice a day; *IV*, intravenous.

Pegylated urate oxidase shows promise in patients with hyperuricemia and gout.[22]

When diagnosed early, gout can be managed and the patient maintained comfortably. The author has a number of patients on long-term gout medications. As long as the owners remember to administer the drugs, the pets do fine. On the rare occasion when the owner forgets, runs out of the prescription, or for some reason does not give the medication, the patients often have quick relapses.

REFERENCES

1. Lewis LD, Morris ML, Hand MS: *Small animal clinical nutrition III*, Topeka, Kan, 1987, Mark L. Morris Associates.
2. Fam AG: Strategies for treating gout and hyperuricemia, *J Musculoskel Med* 5(3):83, 1988.
3. German DC, Holmes EW: Gout and hyperuricemia: diagnosis and management, *Hosp Pract* 21(11):119, 1986.
4. Lo B: Hyperuricemia and gout (topics in primary care medicine), *West J Med* 142:104, 1985.
5. McCance KL, Huether SE: *Pathophysiology: the biological basis of disease in adults and children*, St Louis, 1990, Mosby.
6. Smyth CJ: Monoarticular arthritis: suspect gout, *Diagnosis* 86, 1987.
7. Vawter RL, Spadaro Antonelli MA: Rational treatment of gout, *Postgrad Med* 91(2):115, 1992.
8. Wolfe F: Gout and hyperuricemia, *AFP* 43(6):2141, 1991.
9. Kolle P, Hoffman R: Incidence of nephropathies in European Tortoises, *Proc Assoc Rept Amphib Vet* 33-35, 2002.
10. Lehninger AL: *Biochemistry*, New York, 1975, Worth Publishers.
11. Ganong WF: *Review of medical physiology*, Los Altos, Calif, 1981, Lange Medical Publications.
12. Dessauer HC: Blood chemistry of reptiles: physiological and evolutionary aspects. In Gans C, editor: *Biology of the Reptilia*, San Diego, 1970, Academic Press.
13. Dantzler WH: Comparative aspects of renal urate transport, *Kidney Int* 49:1549-1551, 1996.
14. Campbell TW, Coles EH: Avian clinical pathology. In Coles EH, editor: *Veterinary clinical pathology*, Philadelphia, 1986, WB Saunders.
15. Wenker CJ, Bart M, Guscetti F, Hatt J, Isenbugal E: Periarticular hydroxyapatite deposition disease in two Red-bellied Short-necked Turtles *(Emydura albertisii)*, *Proc Am Assoc Zoo Vet* 23-26, 1999.
16. Frye FL: *Biomedical and surgical aspects of captive reptile husbandry*, Melbourne, Fla, 1991, Krieger Publishing.
17. Casimire-Etzioni AL, Wellehan AFX, Embury JE, Terrell SP, Raskin RE: Synovial fluid from an African Spur-thighed Tortoise *(Geochelone sulcatta)*, *Vet Clin Path* 33(1): 43-46, 2004.

18. Kolle P: Efficacy of allopurinol in European Tortoises with hyperglycemia, *Proc Assoc Rept Amphib Vet* 185-186, 2001.
19. Figureres JM: Treatment of articular gout in a Mediterranean Pond Turtle *(Mauremys leprosa)*, *Assoc Rept Amphib Vet* 7(4): 5-7, 1997.
20. Martin-Silvestre A: Treatment with allopurinol and probenecid for visceral gout in a Greek Tortoise *(Testudo graeca)*, *Assoc Rept Amphib Vet* 7(4):4-5, 1997.
21. Becker MA, Schumacher HR, Wortman RL, et al: Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout, *Arthritis Rheum* 52(3):216-223, 2005.
22. Bomalaski JS, Clark MA: Serum uric acid–lowering therapies: where are we heading in management of hyperuricemia and the potential role of uricase, *Curr Rheumatol Rep* 6(3):240-247, 2004.