REVIEW: PATHOLOGY OF THE REPTILE INTEGUMENT

Drury Reavill, DVM, Dipl ABVP (Avian), Dipl ACVP and Robert Schmidt, DVM, PhD, Dipl ACVP

Zoo/Exotic Pathology Service, 2825 KOVR Drive, West Sacramento, CA 95605 USA

ABSTRACT

The skin is an important anatomic boundary between the environment and the animal. Common insults to this system include infectious agents, neoplastic changes, nutritional imbalances, traumatic injuries, and dermal manifestation of systemic disease. This review will cover a variety of reptile skin diseases described.

Normal Anatomy

In general, the normal reptile integument consists of the outer epidermis and the underlying dermis. The epidermis in reptiles supports the keratin layer, which varies in thickness on the different areas of the animal's body. This keratin forms the scales, which represent a folding of epidermis and for the most part cover most of the reptile's skin. The greatest folding of these scales is seen in snakes where the adjacent scales overlap and are joined by a flexible hinge. The skin of reptiles is covered by alpha or beta keratin or combinations of the two. The dermis consists of connective tissue and possibly osteoderms, depending on the species.[1]

In chelonians, the shell, which consists of the dorsal carapace and ventral plastron has specialized epidermal parts called scutes. The epidermal component of each scute is of beta keratin that covers a continuous layer of pseudostratified columnar epithelial cells. These scutes, which overlay dermis, are generally ossified.

Ecdysis and Dysecdysis

Ecdysis is the periodic shedding or molting of the outer keratinized layer of the epidermis. Crocodilians and chelonians shed continuously in small pieces or sheets of their keratin layer. The squamates, which include lizards and snakes, shed on a cyclic basis and lose the entire outer layer of skin. The process starts with the stratum germinativum forming three new layers with an increase in lymph accumulating between the outer old and the new layer.

Dysecdysis is the abnormal or impaired shedding of the reptile's outer layer of skin. The appearance is of dry flaking skin or skin firmly attached to the underlying new skin. It is a very common problem with deficiencies in the husbandry. Causes include hypoproteinemia leading to inadequate enzyme production, dehydration, traumatic injuries, parasitism, neoplasia and infectious diseases.

Non-infectious Skin Diseases

A variety of non-infectious skin problems can be determined by biopsy. Biopsies of affected skin should be taken from grossly affected areas, particularly if there are any underlying swellings or if there is any associated ulceration or apparent inflammation. In many cases, a definitive diagnosis is only made by histologic examination.

Blistered skin or skin with small bulla may be due to reptiles housed in moist environments.[1] These lesions can be differentiated from infections by histologic examination.

Several nutritional problems can manifest themselves with skin lesions. Vitamin A deficiency may be seen in aquatic and box turtles. This can lead to edema of the eyelids and hyperkeratosis of the mucocutaneous junction of the mouth.[2] Histologically there is epithelial metaplasia and excessive keratosis of the nasal sinuses and conjunctiva of the eye, with a bilateral otitis media. Squamous metaplasia has also been described of the pancreatic ducts and renal collecting ducts.

Hypervitaminosis A may result in very dry skin with some sloughing of superficial layers in tortoises.[3] Detachment of the epithelium is seen histologically as division at the stratum corneum from the stratum germinativum. In addition, there was subcorneal acantholysis, intercellular edema, and acanthosis.

Deficiency of vitamin A in green anoles, *Anolis carolinensis*, has lesions of focally thickened lips, ulcerative cheilitis, swollen eyes, lethargy, depression, and weight loss.[4] In these anoles the squamous metaplasia was present in the oral mucus glands, palpebral conjunctiva, and respiratory mucus membranes of the nasal cavity.

Vitamin E deficiency is the cause of steatitis in several reptile species. This condition usually presents as firm swellings that are yellow-orange within the subcutis.[5]

A shell disease of unknown etiology has been seen in turtles with elevated lesions of the carpace consisting of fibrous scar tissue that is continuous with the dermis and extends among the bone trabeculae. Intervening cystic epidermal structures contain keratin and bone fragments, debris, and possibly bacteria. A variable inflammatory response is noted. The exact pathogenesis of the condition has not been determined.[6] Another condition of undetermined etiology has been described as cutaneous dyskeratosis of desert tortoises, *Gopherus agassizii*.[7] The gross lesions in the shell are gray-white, dry, roughened and flaky. They appear to be superficial. Histologically, there is loss of structural integrity of the horny material overlying the epithelial cells on the scutes and the affected scutes are fragmented.

Calcinosis cutis and calcinosis circumscripta has been described in turtles and lizards.[8-10] Calcinosis cutis is an uncommon process characterized by inappropriate deposition of inorganic calcium and phosphate ions with smaller amounts of iron, magnesium, or other mineral salts, in the dermis, epidermis, or subcutis. Calcinosis circumscripta is a clinical subgroup of calcinosis cutis that is characterized by the deposition of calcium salts in tumor-like nodules, usually in the

subcutaneous tissues. Both turtles (Geoffrey's side-necked turtle, *Phrynops geoffroanus*, and Malayan box turtle, *Cuora amboinensis kamaroma*) presented with areas of thickened skin primarily noted on the limbs.[8,9] The skin lesions in both cases were interpreted as calcinosis circumscripta. Significant renal lesions were also present, suggesting the cause was a disorder of calcium metabolism due to renal failure (dystrophic mineralization). Four of the lizards were old World chameleons (crested chameleon, *Chamaeleo cristatus*, panther chameleon, *C. pardalis*, veiled chameleon, *C. calyptratus*, and a chameleon, species not provided). The remaining lizards are two *Uromastyx*, species unknown, a bluetongue skink, *Tiliqua* sp. and a Komodo dragon, *Varanus komodoensis*.[10] The lesions were local swellings to multifocal crusty skin thickenings, ulcerations, sloughing scales and occasionally petechial hemorrhages over the body, feet, legs and tail. The discrete masses were filled with a white liquid crystalline material. By serum chemistry findings and the urate granulomas closely associated with the mineralized lesions in a few cases, it was felt renal disease was an important underlying cause.

Infectious Skin Diseases

Non-neoplastic skin diseases/swellings can be either infectious or non-infectious. Biopsy of these lesions is necessary for making a definitive diagnosis and either finding the causative organism or the histologic changes indicating that these lesions are inflammatory but not infectious. The infectious agents include viruses, bacteria, fungi, and protozoan and metazoan parasites. Parasitic dermatitis will not be covered in this review.

Infectious skin disease can present as solitary or multiple swellings that in some cases can mimic neoplasms. These lesions generally are chronic abscesses or granulomas, characterized histologically by a necrotic center, which may contain the causative organism, surrounded by a pleocellular inflammatory infiltrate and a connective tissue capsule. In general, multifocal to disseminated skin disease is usually grossly characterized by reddening, thickening of the skin, variable necrosis/ulceration and crust formation.[11]

Viral Dermatosis

Herpesvirus

Erosive and ulcerative skin lesions are described on the extremities of a Russian tortoise, *Agrionemys horsfieldii*, following hibernation and were linked to a herpesvirus infection. Viral intranuclear inclusions were present in the skin sections.[12]

Fibropapillomatosis of green sea turtles, *Chelonia mydas*, is a well recognized and studied disease. The etiology remains uncertain; however, several studies have suggested a role for a herpesvirus, which has been informally called chelonid fibropapilloma-associated herpesvirus (CFPHV).[13,14]

Papillomavirus

Papillomavirus-like particles have been identified associated with skin lesions of sideneck turtles, *Platemys platycephala*, and European green lizards, *Lacerta viridis*.[15-17] In the sideneck turtles, these presented as small round to confluent white skin lesions over the head. Hyperkeratosis and hyperplasia of the epidermis were noted. On ultrastructural evaluation, there were crystalline aggregates of the virus within the nuclei of the cells, which were interpreted as papillomaviruses. The lesions were benign and resolved within 6 mo. The European green lizards developed the typical squamous papillomas as solitary or multiple raised gray-white lesions on the dorsum of the body. In addition to viral particles identified and interpreted as papillomavirus by electron microscopy there were also herpesvirus-like and reovirus-like particles.[15,16]

A papillomavirus was isolated and characterized from a proliferative dermatitis in a loggerhead turtle, *Caretta caretta*, and a green turtle, *Chelonia mydas*.[18] Both were young animals with small, white raised lesions on the flippers and over the neck and shoulders of the loggerhead turtle. Histopathologically these were multifocal areas of epidermal hyperplasia with a few intranuclear inclusions in some cells. Further work by transmission electron microscopy, polymerase chain reaction (PCR) diagnostics characterized two novel papillomaviruses. The lesions resolved over several months.

Poxvirus

Poxvirus dermatitis has been more frequently reported in the order Crocodilia.[19-23] The lesions are grossly described as macules to warts developing on the skin, especially over the head and neck and in the oral cavity. The outbreaks were usually in juvenile animals. The typical large eosinophilic intracytoplasmic inclusions were recognized histologically within epithelial cells.

The only saurian case of poxviral dermatitis is described in a captive tegu lizard, *Tupinamobis teguisini*.[24] The lesions resolved within 3 – 4 mo without therapy.

A captive Hermann's tortoise, *Testudo hermanni*, developed white-yellow popular lesions on the lower eyelid and on the left side of the rostrum. The tortoise died after suffering anorexia and weight loss. Histologic lesions with the intracytoplasmic inclusions and ultrastructural evidence of viral particles typical for poxvirus were identified.[25]

Bacteria

A variety of bacteria have been associated with dermal disease in captive reptiles although their role as primary etiologic agents is questionable.[1] Predisposing factors play a major role in the development of bacterial and fungal dermatitis. These include environmental mismanagement (humidity, temperature, social stress) or other diseases (gastrointestinal, respiratory, ectoparasites).

Septicemic Cutaneous Ulcerative Dermatitis (SCUD)

Septicemic cutaneous ulcerative dermatitis (SCUD) is also known as shell rot. The etiologic agent of SCUD is the gram- negative bacterium *Citrobacter freundii*, but other bacteria such as *Aeromonas hydrophila*, *Beneckea chitinovora,* and *Serratia* species have been associated with ulcerative lesions in freshwater turtles.[26]   The disease causes cutaneous ulceration, anorexia, lethargy, hepatic necrosis and finally death.[27] Poor nutrition and maintenance in contaminated water are the suspected origin of the disease. In addition, bacteria of the genus *Serratia* are able to secrete proteolytic enzymes and may contribute to the origin of the disease allowing the entry of other etiologic agents through the skin.[26]

Dermatophilus

Dermatophilosis is a cutaneous infectious disease that is caused by a gram-positive, periodic acid-schiff (PAS) positive, and acid fast-negative coccoid bacterium belonging to the family of Dermatophilaceae. It has a unique branching, filamentous morphology in lesions. There may be specific Dermatophilus species adapted to poikilothermic animals. *Dermatophilus chelonae* is proposed for 3 chelonian isolates from Australia.[28]

This has been described as a significant pathogen in a variety of lizards, a boa constrictor, *Constrictor constrictor*, American alligator, *Alligator mississippiensis*, crocodiles, and tortoises.[28-34]   The lesions are of hyperkeratosis, inflammation, and epidermal necrosis with some cases developing caseous subcutaneous nodules.[29-34]

Devriesea agamarum

The bacterium, *Devriesea agamarum* has been isolated and characterized from *Uromastyx* species with dermatitis and/or septicemia.[35-37]   This facultative pathogenic bacterium is able to cause dermatitis in agamid lizards (*Agama impalearis*, *Pogona vitticeps*, *Uromastyx geyri*, and *Uromastyx acanthinura*) when the integrity of the skin is breached. The lesions that develop are a proliferative dermatitis and/or cheilitis.[37]   The bacterium is a Gram-positive small rod that by comparative analysis of 16S rRNA gene sequences was identified as a strain in the new taxon within the class Actinobacteria.[35] In further studies *D. agamarum* was found to be part of the oral microbiologic flora in *Pogona vitticeps*.[36]

Mycobacteria

Mycobacteriosis has been uncommonly described as a cause of dermatitis in reptiles. In the few cases reported in chelonians, (sideneck turtle, *Phrynops hilari*, Chinese soft shell turtle, *Pelodiscus sinensis*) granulomatous inflammation and organisms were present in the skin, which suggested a cutaneous route of entry with hematogenous spread to visceral organs.[38,39] *Mycobacterium kansasii* was the isolated from the Chinese soft shell turtle. In a boa constrictor the lesions were of a stomatitis and subcutaneous granulomas. *M. chelonei* was identified.[40]

Fungus

The fungal dermatoses of reptiles mimic bacterial dermatitis with mixed infections being common. The skin/shell lesions may appear as brown to greenish yellow discolorations and develop into blisters, ulcers, nodules, crusts, soft spots in the shell, granulomas, or swollen limbs. Most reports of skin infection in chelonians, lizards, and snakes are attributed to a wide variety of soil fungi. [41]

Aspergillus

Aspergillosis produced chronic extensive dermal granulomas in two San Esteban chuckwallas, *Sauromalus varius*.[42] These lesions progressed through the body wall and into the cerebrum and the lung.

Chrysosporium anamorph of *Nannizziopsis vriesii*

Chrysosporium anamorph of *Nannizziopsis vriesii* (CANV), a dermatophyte-like fungus was isolated from skin biopsies of three different species of captive adult chameleons and bearded dragons, *Pogona vitticeps*.[43,43a] A Parson's chameleon, *Chamaeleo parsonii*, presented with vesicles that became crusty brown lesions on the limbs and body in which fungal elements had been observed by histologic examination. One adult jewel chameleon, *Chamaeleo lateralis*, in this collection developed black skin lesions and died with a pulmonary fungal granuloma. A third isolate was obtained from a skin biopsy of a Jackson's chameleon, *Chamaeleo jacksoni*, with deep ulcerative cutaneous lesions located at the base of the tail. The bearded dragons developed deep granulomatous dermatitis. All died; however, only one was examined further and it had a granulomatous hepatitis with intralesional hyphae.

Fatal CANV mycotic dermatitis occurred in captive brown tree snakes, *Boiga irregularis*.[44] All snakes died within 14 days after clinical signs were first noted. The first lesions developed on the ventral scales and began as areas of erythema and edema with vesicle formation, followed by development of caseous brown plaques. The fungus was identified as the *Chrysosporium anamorph* of *Nannizziopsis vriesii*, described previously in chameleons and bearded dragons. The same fungus was identified as the cause of fatal, multifocal, heterophilic dermatitis in four freshwater aquatic captive-bred tentacled snakes, Erpeton tentaculatum.[44a] In these animals the lesions occurred primarily on the head and dorsum.

Chromomycosis

Two box turtles, *Terrapene carolina*, were diagnosed with a dermatitis due to the pigmented fungus (chromomycosis). [45] Chromomycosis is primarily a systemic fungal infection caused by pigmented fungi of the family Dematiaceae. These fungi are saprophytes that live in soil and decaying vegetable matter, predominantly in warmer climates of tropical and subtropical countries. Some identified members include *Cladosporium herbarum*, *Scolecobasidium humicola*, *Fonsecaea* spp., *Phialophora* spp., *Rhinocladiella* spp., *Hormodendrum* spp.,

Curvularia spp., and *Drechslera* spp. The fungal organisms produce a characteristic amber-brown, thick-walled, septate structures known as sclerotic bodies.

Scolecobasidium humicola, a soil fungus and etiologic agent of phaeohyphomycosis in fish (a systemic infection) was the cause of cutaneous lesions in Eastern box turtles, *Terrapine carolina var. carolina*.[46] These turtles developed both granulomatous and ulcerated papules on the feet and tail.

Cryptococcus

Cryptococcosis has produced skin lesions in a variety of lizards. An Eastern water skink, *Eulamprus quoyii* presented for a small, discrete, painless mass over the lower thoracic spine. [47] Numerous vacuoles of various sizes separated by fibrovascular stroma contained yeast structures.

Yeast

Cutaneous geotrichosis in a giant tortoise, *Geochelone elephantopus*, appeared as an ulcerative skin lesion on all legs and on lower and lateral surfaces of the neck and head.[48] After death, the fungal hyphae and spores were identified in the skin and kidney. It was felt the fungus was disseminated from the skin lesions to the kidneys. Culture of these tissues yielded *Geotrichum candidum*, a common environmental contaminant.

Mycotic granulomata with many yeast-like organisms and pseudohyphae, resulted in ulcerated forefeet in a musk turtle, *Sternotherus odoratus*. The granulomas extended into the muscle.[49]

The fungal organism causing a mycotic dermatitis in a black ratsnake, *Elaphe obsoleta* was identified as *Monilia sitophila*, an organism previously considered to be non-pathogenic, and a troublesome laboratory contaminant.[50] The lesions were of dull and roughened scales that expanded and coalesced to involve extensive areas.

In a series of six snakes with mycotic dermatitis, four had concurrent *Pseudomonas* bacteria isolated from the skin lesions.[51] The fungal organisms were suspected to be environmental contaminates and suboptimal environmental temperature a contributing factor in the development of disease. Death of snakes due to skin lesions was believed to be related to disruption of normal cutaneous barrier, allowing body fluid and electrolyte loss through damaged skin. Fungal or bacterial toxemia may also be a factor.

Other Fungus

Fungal shell infections have been reported in desert tortoises, *Gopherus agassizii* and Florida softshell turtles, *Trionyx ferox*.[52,53] In the tortoises, lesions included necrotic shells with multiple foci of cell debris and heterophilic inflammation within the epidermal horn layer that were subtended by necrotic dermal bone colonized by both bacteria and fungi. *Mucor* sp. caused an ulcerative epidermitis in the softshell turtles. The turtles presented with circular grey skin lesions

on the body including the carapace and plastron. Most died within 2 wk. Fungal hyphae and bacteria were confined to the epidermis. Death in these turtles was suspected to be due to osmotic imbalance due to loss of the epidermal barrier.

Fusarium species are common soil saprophytes and plant pathogens. In one report *Fusarium solani* was determined to be the agent of a cutaneous infection in an injured loggerhead sea turtle, *Caretta caretta L.*[54] With topical and systemic therapy the lesions resolved. A fungal dermatitis in a yellow-bellied sea snake, *Pelamis platurus*, was associated with the lesions of multifocal, erosive and ulcerative dermatitis with pustules occurring within the overlying epithelium and caused by *F. solani*. The pustules were characterized by aggregates of heterophils with associated hemorrhage, fibrin, and edema separating the layers of the stratified squamous epithelium. Within foci, there were large numbers of proliferating fungal organisms.[55]

A corn snake, *Elaphe guttata*, two timber rattlesnakes, *Crotalus horridus*, and bull snake, *Pituophis catenifer sayi*, developed disseminated and fatal infections of a zygomycete fungus.[56] All snakes had granulomas in the subcutis and visceral tissues. Although the portal of entry was not discussed, three snakes had skin or oral lesions and one has disseminated disease that was prominent in the gastrointestinal tract.

Neoplasia

Epithelial tumors include papillomas and squamous cell carcinomas. Papillomas often present as solitary or multiple raised gray-white lesions. They have been identified on several reptiles including a common snapping turtle, *Chelydra serpentina*, common boa, mata mata, *Chelys fimbriatus*, Haitian boa, *Epipcrates striatus striatus*, and red-eared slider turtle, *Trachemys scripta elegans*; several have been linked to viral etiologies (see previous).[57,58] Histologically, reptilian papillomas are often characterized as resembling early changes as seen in mammals. The overlying epidermis is hyperplastic and hyperkeratotic. Viral inclusions are not seen on typical histologic sections or with inclusion body stains. Electron microscopy and/or PCR diagnostics are necessary for characterization of the virus.[15,57]

Squamous cell carcinoma (SCC) is uncommon in reptiles. The primary tumor sites are of the skin and oral cavity. Cutaneous SCCs appear as proliferative, irregular, broad-based masses or wound-like ulcers. Generally, the neoplastic cells form nests and cords that are infiltrative into the surrounding tissues. Reports include a periorbital mass in a veiled chameleon, *Chamaeleo calyptratus* and an Eastern box turtle, *Terrapene carolina* that developed a squamous cell carcinoma at the site of a forelimb amputation.[59,60] SCCs are locally aggressive; however, metastases were not reported in the few documented reptile cases.

Fibrosarcomas originate from fibrous connective tissue and myxosarcomas are variant fibrosarcomas which arise from primitive pleomorphic fibroblasts and produce excessive mucin. Diagnosis is generally made by examination of hematoxylin-eosin stained tissue sections. However, these two tumor-types are part of the family of soft tissue spindle cell sarcomas (including leiomyosarcoma, liposarcoma, neurofibrosarcoma, schwannoma, ganglioneuroma,

and ganglioneuroblastoma) and as they become less well differentiated they may have significant overlap of morphologic features. More definitive determination of the tissue of origin can require immunohistochemistry and electron microscopy. Fortunately, in many species, these tumors have similar biologic behavior.

In snakes, fibrosarcomas and myxosarcomas most commonly affect the subcutaneous intermandibular tissues, while they are more frequently recognized within the subcutis and muscle tissues in chelonians and saurians. The tumor masses are firm with irregular and indistinct borders. Fibrosarcomas and myxosarcomas are locally invasive, do not commonly metastasize, and have a moderate to high potential for recurrence. In Burmese pythons, *Python molurus bivattatus*, type C-like retroviral particles were found in an intermandibular fibrosarcoma.[61] This can suggest a possible viral etiology; however, retroviral type particles have also been identified in other tumor types.

Lipomas and infiltrative lipomas are benign connective tissue tumors that are infrequently described in reptiles. The majority of reports have been of infiltrative lipomas in corn snakes, *Elaphe guttata*, and the tumors have generally been located in the caudal one third of the body.[62,63] The infiltrative lipoma has a locally aggressive behavior and can be difficult to completely remove. A common complication is obstipation due to the mass effect.

A smaller number of lipomas have been described. Reports include masses in the subcutis of boa constrictors.[64] Grossly lipomas are soft, pale yellow, encapsulated, and lobulated. Histologically they are indistinguishable from normal adipose tissue. If lipomas are traumatized, they may become inflamed and necrotic.

Liposarcomas, malignant tumors of lipocytes and lipoblasts, are rare. They have been described in Burmese python, *Python molurus bivittatus*, shingleback skink, *Trachydosaurus rugosu*, boa constrictor, and veiled chameleon, *Chamaeleo calyptratus*.[65,66] They appear as yellow to gray poorly circumscribed masses of the subcutis and differ from lipomas in that they are firmer, more infiltrative and vascular. Liposarcomas are expected to be aggressive and in two reports they presented as multiple subcutaneous masses. Diagnosis depends on a surgical biopsy. Immunohistochemistry and electron microscopy may be important contributing diagnostic tests. The proposed therapy is wide and aggressive surgical excision.

Chromatophoromas are common neoplasms of pigment-producing chromatophores. They are described from within the subcutis of snakes[67-72] and lizards.[64,73,74] Tumors may arise from melanophores (melanin pigment producing cells), iridophores (cells with birefringent intracytoplasmic particles that refract and reflect light), erythrophores (red/orange pigment producing cells) and xanthophores (which produce yellow pigments). Although most of these tumors involve only one type of pigment cell, multiple pigment cell types have been involved in some cases. Generally the morphologic features described for chromatophoromas are similar to those of malignant melanomas in higher vertebrates. Grossly, tumors are variable in size, multilobulated, and may be partially encapsulated. They can vary from orange to red to black.

Of the several cases of chromatophoromas (or melanomas) reported in snakes, most have been malignant with local invasion, local recurrence, and/or distant metastases (esophagus, pericardium, coelom). Rare cases have been described in lizards and these few reports do not describe metastasis[64,74] with the exception of one veiled chameleon, *Chamaeleo calyptratus.*[73]

Although mast cell tumors are among the most common skin neoplasms of domestic canines, felines, and ferrets, they are rare in reptiles. A single case has been reported in an Eastern king snake (*Lampropeltis getulus getulus*).[75] This snake presented with a poorly differentiated cutaneous tumor which was locally aggressive with neoplastic lymphatic emboli and multi-organ metastasis. Treatment was attempted; however, the snake died after the start of radiation therapy. There are rare reports of well-differentiated, multicentric cutaneous and mucosal mast cell tumors with peripheral blood mastocytosis in iguanas, *Iguana iguana.*[76] The reported masses were subcutaneous, firm, and white in color. A well-differentiated cutaneous mast cell tumour was diagnosed in a subadult female giant Galapagos tortoise.[77] The tumor was a pedunculated, verrucose mass located near the base of the neck. The histologic features, which were diagnostic for a mast cell tumour, included abundant intracytoplasmic granules that were stained metachromatically with Giemsa and toluidine blue stains. Although the neoplastic cells extended to the surgical margins, the tortoise was reported well 11 mo later. These must be differentiated from the more common bacterial or fungal granulomas and cutaneous lymphosarcomas. Effective therapy has not been reported.

LITERATURE CITED

1. Jacobson, E.R. 1992. Reptile dermatology. In: Miller RE (ed). Current Veterinary Therapy XI SAP, Philadelphia, W. B. Saunders. Pp 1204-1210.
2. Holladay, S.D., J.C. Wolf, S.A. Smith, D.E. Jones, and J.L. Robertson. 2001. Aural abscesses in wild-caught box turtles (*Terapene carolina*): possible role of organochlorine-induced hypovitaminosis A. Ecotoxicol Environ Saf. 48(1):99-106.
3. Palmer, D.G., A. Rubel, F. Mettler, and L. Volker. 1984. [Experimentally induced skin changes in tortoises by high parenteral doses of vitamin A]. Zentralbl Veterinarmed A. 31(8):625-633. [Article in German]
4. Miller, E.A., S.L. Green, G.M. Otto, D.M. Bouley. 2001. Suspected hypovitaminosis A in a colony of captive green anoles (*Anolis carolinensis*). Contemp. Topics Lab. Anim. Sci. 40(2):18-20.
5. Larsen, R.E., C. Buergelt, P.T. Cardeilhac, and E.R. Jacobson. 1983. Steatitis and fat necrosis in captive alligators. J. Am. Vet. Med. Assoc. 183(11):1202-1204.
6. Lovich, J.E., S.W. Gotte, C.H. Ernst, J.C. Harshbarger, et al. 1996. Prevalence and histopathology of shell disease in turtles from lake blackshear, Georgia. J. Wildl. Dis. 32(2):259-265.
7. Jacobson, E.R., T.J. Wronski, J. Schumacher, C. Reggiardo, et al. 1994. Cutaneous dyskeratosis in free-ranging desert tortoises, *Gopherus agassizii*, in the Colorado desert of southern California. J. Zoo Wildl. Med. 25(1):68-81.
8. Raiti, P., and M.M. Garner. 2006. Metastatic Mineralization in a Geoffrey's side-necked turtle, *Phrynops geoffroanus*. J. Herpetol. Med. Surg. 16(4):135-139.

9. Yani, T., A. Noda, K. Hasegawa, H. Sakai, and T. Masegi. 2002. Calcinosis circumscripta in a Malayan box turtle (*Cuora amboinensis kamaroma*). Proc. 6th Int. Symp. Pathol. Reptiles Amphibian. 111-115.

10. Reavill, D.R. 2002. Mineralized skin lesions in lizards. Proc. Assoc. Reptilian Amphibian Vet. 77-78.

11. Reavill, D.R., and R.E. Schmidt. 2000. Reptile Surgical Pathology. In: Fudge, A.M. (ed.). Laboratory Medicine: Avian and Exotic Pets, W. B. Saunders, Co. Pp. 236-242.

12. Fischer, S., K. Strutzberg-Minder, G. Müller, and M. Homuth. 2006. [Molecularbiological diagnosis of herpes virus infection of a juvenile Russian tortoise (*Agrionemys horsfieldii*) with skin and lung lesions]. Berl Munch Tierarztl Wochenschr. 119(1-2):28-34. (German).

13. Jacobson, E.R., C. Buergelt, B. Williams, and R.K. Harris. 1991. Herpesvirus in cutaneous fibropapillomas of the green turtle, *Chelonia mydas*. Dis. Aquat. Organ. 12:1–6.

14. Herbst, L.H., E.R. Jacobson, P.A. Klein, G.H. Balazs, R. Moretti, T. Brown, and J.P. Sundberg. 1999. Comparative pathology and pathogenesis of spontaneous and experimentally induced fibropapillomas of green turtles (*Chelonia mydas*). Vet. Pathol. 36:551–564.

15. Jacobson E.R., J.M. Gaskin, S. Clubb, and M.B. Calderwood. 1982. Papilloma-like virus infection in Bolivian side-necked turtles. J. Am. Vet. Med. Assoc. 181(11):1325-1328.

16. Raynaud, A., and M. Adrian. 1976. Lesions cutanees a structure papillomateuse associees a des virus chez le Lezard vert (*Lacerta viridis* Laur). C.R. Acad. Sci. (Paris) 283D: 845–847.

17. Cooper, J.E., S. Gschmeissner, and P.E. Holt. 1982. Viral particles in a papilloma from a green lizard (*Lacerta viridis*). Lab. Anim. 16(1):12-13.

18. Manire, C.A., B.A. Stacy, M.J. Kinsel, T. Heather. H.T. Daniel, E.T. Anderson, and J.F.X. Wellehan Jr. 2008. Proliferative dermatitis in a loggerhead turtle, *Caretta caretta*, and a green turtle, *Chelonia mydas*, associated with novel papillomaviruses. Vet. Microbiol. 130:227–237.

19. Penrith, M.L,, J.W. Nesbit, and F.W. Huchzermeyer. 1991. Pox virus infection in captive juvenile caimans (*Caiman crocodilus fuscus*) in South Africa. J. S. Afr. Vet. Assoc. 62(3):137-9.

20. Huchzermeyer, F.W., K.D. Huchzermeyer, and J.F. Putterill. 1991. Observations on a field outbreak of pox virus infection in young Nile crocodiles (*Crocodylus niloticus*). J. S. Afr. Vet. Assoc. 62(1):27-9.

21. Gerdes, G.H. 1991. Morphology of poxviruses from reptiles. Vet. Rec. 128(19):452.

22. Horner, R.F. 1988. Poxvirus in farmed Nile crocodiles. Vet. Rec. 122(19):459-62.

23. Jacobson, E.R., J.A. Popp, R.P. Shields, and J.M. Gaskin. 1979. Poxlike skin lesions in captive caimans. J. Am. Vet. Med. Assoc. 175(9):937-40.

24. Stauber, E., and R. Gogolewski. 1990. Poxvirus dermatitis in a tegu lizard (*Tupinambis teguixin*). J. Zoo Wildl. Med. 21(2):228-230.

25. Orós, J., J.L. Rodríguez, L. Déniz S, Fernández, and A. Fernández. 1998. Cutaneous poxvirus-like infection in a captive Hermann's tortoise (*Testudo hermanni*). Vet. Rec. 143(18):508-509.

26.   Boyer, T.H. 1996. Turtles, tortoises and terrapins. In: Mader, D. (ed.). Reptile Medicine and Surgery. WB Saunders, Toronto, Pp. 332 – 333.

27.   Barten, S.L. 1996. Shell damage. In: Mader, D. (ed.). Reptile Medicine and Surgery. WB Saunders, Toronto, Pp. 413 – 415.

28.   Masters, A.M., T.M. Ellis, J.M. Carson, et al. 1995, *Dermatophilus chelonae* sp. nov., isolated from chelonids in Australia. Int. J. Syst. Bacteriol. 45:50 –56.

29.   Montali, R.J., E.E. Smith, M. Davenport, et al. 1975. Dermatophilosis in Australian bearded lizards. J. Am. Vet Med. Assoc. 167: 553–555.

30.   Anver, M.R., J.S. Park, and H.G. Rush. 1976. *Dermatophilus* in the marble lizard (*Calotes mystaceus*). Lab. Anim. Sci. 26:817–823.

31.   Simmons, G.C., N.D. Sullivan, and P.E. Green. 1972. *Dermatophilus* in a lizard (*Amphibolurus barbatus*). Aust Vet. J. 48:465– 466.

32.   Buenviaje, G.N., P.W. Ladds, and Y. Martin. 1998. Pathology of skin diseases in crocodiles. Aust. Vet. J. 76(5):357-63.

33.   Jacobson, E.R. 1991. Diseases of the integumentary system of reptiles. In: Dermatology for the small animal practitioner, exotics, feline, canine, Nesbitt,G.H. and L.J. Ackerman (eds.). Veterinary Learning Systems, Trenton, NJ. Pp. 225-239.

34.   Bemis, D.A., C.S. Patton, and E.C. Ramsay. 1999. Dermatophilosis in captive tortoises. J. Vet. Diagn. Invest. 11:553–557.

35.   Martel, A., F. Pasmans, T. Hellebuyck, F. Haesebrouck, and P. Vandamme. 2008. *Devriesea agamarum* gen. nov., sp. nov., a novel actinobacterium associated with dermatitis and septicaemia in agamid lizards. Int. J. Syst. Evol. Microbiol. 58:2206–2209.

36.   Hellebuyck, T., A. Martel, K. Chiers, F. Haesebrouck, and F. Pasmans. 2009. Devriesea agamarum causes dermatitis in bearded dragons (*Pogona vitticeps*). Vet. Microbiol. 134(3-4:267-271.

37.   Koplos, P., M. Garner, T. Besser, R. Nordhausen, and R. Monaco. 2000. Cheilitis in lizards of the genus *Uromastyx* associated with a filamentous gram positive bacterium. Proc. Assoc. Reptilian Amphibian Vet. Pp. 73–75.

38.   Orós, J., B. Acosta, J.M. Gaskin, S. Déniz, and H.E. Jensen. 2003. *Mycobacterium kansasii* infection in a Chinese soft shell turtle (*Pelodiscus sinensis*). Vet. Rec. 152(15):474-6.

39.   Rhodin, A.G., and M.R. Anver. 1977. Myobacteriosis in turtles: cutaneous and hepatosplenic involvement in a *Phrynops hilari*. J. Wildl. Dis. 13(2):180-183.

40.   Quesenberry, K.E., E.R. Jacobson, J.L. Allen and A.J. Cooley. 1986. Ulcerative stomatitis and subcutaneous granulomas caused by *Mycobacterium chelonei* in a boa constrictor. J. Am. Vet. Med. Assoc. 189:1131-1132.

41.   Rossi, J.V. 1996. Dermatology. In: Mader, D.R. (ed.). Reptile Medicine and Surgery. W.B. Saunders Co., Philadelphia, Pennsylvania. Pp 112.

42.   Tappe, J.P., F.W. Chandler, S. Liu, and E.P. Dolensek. 1984. Aspergillosis in two San Esteban chuckwallas. J. Am. Vet. Med. Assoc. 185(11):1425-1428.

43.   Pare, J.A., L. Sigler, D.B. Hunter, R.C. Summerbell, D.A. Smith, and K.L. Machin. 1997. Cutaneous mycoses in chameleons caused by the *Chrysosporium* anamorph of *nannizziopsis vriesii* (*apinis*) *currah*. J. Zoo. Wildl. Med. 28(4):443-453.

43a. Bowman, M.R., J.A. Paré, L. Sigler, J.P. Naeser, K.K. Sladky, C.S. Hanley, P. Helmer, L.A. Phillips, A. Brower, and R. Porter. 2007. Deep fungal dermatitis in three inland bearded dragons (*Pogona vitticeps*) caused by the *Chrysosporium* anamorph of *Nannizziopsis vriesii*. Med. Mycol. 45(4):371-376.

44. Nichols, D.K., R.S. Weyant, E.W. Lamirande, L. Sigler, and R.T. Mason. 1999. Fatal mycotic dermatitis in captive brown tree snakes. J. Zoo. Wildl. Med. 30(1):111-118.

44a. Bertelsen, M.F., G.J. Crawshaw, L. Sigler, and D.A. Smith. 2005. Fatal cutaneous mycosis in tentacled snakes (*Erpeton tentaculatum*) caused by the *Chrysosporium* anamorph of *Nannizziopsis vriesii*. J. Zoo. Wildl. Med. 36(1):82-7.

45. Reavill, D.R., M. Melloy, and R.E. Schmidt. 2004. A review of reptile mycotic infections from the literature and 55 cases. Proc. Assoc. Reptilian Amphibian Vet. Pp 62-71.

46. Weitzman, I., S.A. Rosenthal, and J.L. Shupack. 1985. A comparison between *Dactylaria gallopava* and *Scoleocobasidium humicola*: first report of an infection in a tortoise caused by s. humicola. J. Med. Vet. Mycol. 23:287-293.

47. Hough, I. 1998. Cryptococcosis in an eastern water skink. Aust. Vet. J. 76(7):471-472.

48. Ruiz, J.M., E. Arteaga, J. Martinez, E.M. Rubio, and J.M. Torres. 1980. Cutaneous and renal geotrichosis in a giant tortoise (*Geochelone elephantopus*) Sabouraudia. 18(1):51-59.

49. Frye, F.L., and F.R. Dutra. 1974. Mycotic granulomata involving the forefeet of a turtle. Vet. Med. Sm. Anim. Clin. 12:1554-1556.

50. Dillberger, J., and M. Abou-Gabal. 1979. Mycotic dermatitis in a black ratsnake. Mykosen. 22(6):187-190.

51. Jacobson, E.R. 1980. Necrotizing mycotic dermatitis in snakes: clinical and pathologic features. J. Am. Vet. Med. Assoc. 177(9):838-841.

52. Homer, B.L., K.H. Berry, M.B. Brown, G. Ellis, et al. 1998. Pathology of diseases in wild desert tortoises from California. J. Wildl. Dis. 34(3):508-523.

53. Jacobson, E.R., M.B. Calderwood, and S.L. Clubb. 1980. Mucormycosis in hatchling Florida softshell turtles. J. Am. Vet. Med. Assoc. 177(9):835-837.

54. Cabanes, F.J., J.M. Alonso, G. Castella, F. Alegre, et al. 1997. Cutaneous hyalohyphomycosis caused by *Fusarium solani* in a loggerhead sea turtle (*Caretta caretta* L.). J. Clin. Microbiol. 35(12);3343-3345.

55. Reavill, D.R., G.L. Crow, B. Okimoto. 2004. Fungal dermatitis in a yellow-bellied sea snake (*Pelamis platurus*). Proc. IAAAM. Pg 38-39.

56. Kaplan, W., F.W. Chandler, A.A. Padhye, and T.E. Hamm. 1983. A zygomycotic infection in captive snakes. Sabouraudia. 21:85-91.

57. Raiti, P. 2008. Carbon dioxide (CO2) laser treatment of cutaneous papillomas in a common snapping turtle, *Chelydra serpentina*. J. Zoo Wildl. Med. 39(2):252-6.

58. Frye, F.L. 1991. Biomedical and Surgical Aspects of Captive Reptile Husbandry. Krieger Publishing Co., Malabar, Florida. Pp 580.

59. Abou-Madi, N., and T.J. Kern. 2002. Squamous cell carcinoma associated with a periorbital mass in a veiled chameleon (*Chamaeleo calyptratus*). Vet. Ophthalmol. 5(3):217-220.

60. Greenacre, C.B., and R. Roberts. 2000. Effect of Strontium-90 on Squamous Cell Carcinoma in an Eastern box turtle (*Terrapene carolina*); Discussion of Alternative

Treatment Modalities. International Virtual Conference in Veterinary Medicine (IVCVM), hosted by the University of Georgia College of Veterinary Medicine.

61. Chandra, A.M., E.R. Jacobson, and R.J. Munn. 2001. Retroviral particles in neoplasms of Burmese pythons (*Python molurus bivittatus*). Vet. Pathol. 38(5):561-564

62. Burkert, B.A., T.N. Tully, J. Nevarez, M.A. Mitchell, and A.C. Camus. 2002. Infiltrative lipoma in a corn snake, *Elaphe guttata guttata*. J. Herpetol. Med. Surg. 12;33-35.

63. Reavill, D.R., and R.E. Schmidt. 2003. Lipomas in cornsnakes (*Elaphe guttata guttata*); A series of four cases, Proc. Assoc. Reptilian and Amphibian Vet. 60-61.

64. Hernandez-Divers, S.M., and M.M. Garner. 2003. Neoplasia of reptile with an emphasis on lizards. Vet. Clin. Exotic Anim. 6;251-273.

65. Garner, M., C. Johnson, and R. Funk. 1994. Liposarcoma in a shingleback skink (*Trachydosaurus rugosus*). J. Zoo Wildl. Med. 25(1):150-153.

66. Reavill, D.R., B. Dahlhausen, B. Zaffarano, and R. Schmidt. 2002. Multiple cutaneous liposarcomas in a red-tailed boa, *Boa constrictor*, and veiled chameleon, Chamaeleo *calyptratus*. Proc. Assoc. Reptilian Amphibian Vet. 5-6.

67. Frye, F.L., J.D. Carney, J.C. Harshbarger, and R.F. Zeigel. 1975. Malignant chromatophoroma in a Western terrestrial garter snake. J. Am. Vet. Med. Assoc. 167(7):557-558.

68. Gregory, C.R., B.G. Harmon, K.S. Latimer, S. Hafner, et al. 1997. Malignant chromatophoroma in a canebrake rattlesnake (*Crotalus horridus atricaudatus*). J. Zoo Wildl. Med. 28(2):198-203.

69. Ryan, M.J., D.L. Hill, and G.D. Whitney. 1981. Malignant chromatophoroma in a gopher snake. Vet. Pathol. 18: 827-829.

70. Ramsay, E.C., L. Munson, L. Lowenstein, and M.E. Fowler. 1996. A retrospective study of neoplasia in a collection of captive snakes. J. Zoo Wildl. Med. 27(1):28-34.

71. Kusewitt, D.F., R.L. Reece, and K.B. Miska. 1997. S-100 immunoreactivity in melanomas of two marsupials, a bird, and a reptile. Vet. Pathol. 34(6):615-618.

72. Suedmeyer, W.K., J.N. Bryan, G. Johnson, and A. Freeman. 2007. Diagnosis and clinical management of multiple chromatophoromas in an eastern yellowbelly racer (*Coluber constrictor flaviventris*). J. Zoo Wildl. Med. 38(1):127-30.

73. Reavill, D.R., and R.E. Schmidt. 2004. Malignant chromatophoromas in three veiled chameleons, *Chamaeleo calyptratus*. Proc. Assoc. Reptilian Amphibian Vet. 131-132.

74. Mikaelian, I., S. Lynch, J.C. Harshbarger, and D.R. Reavill. 2000. Malignant chromatophoroma in a day gecko (*Phelsuma madagarescencis grandis*). Exotic Pet Pract. 5(10);1-2.

75. Schumacher, J., R.A. Bennett, L.E. Fox, S.L. Deem, et al. 1998. Mast cell tumor in an eastern kingsnake (*Lampropeltis getulus getulus*). J. Vet. Diagn. Invest. 10: 101-104.

76. Reavill, D.R., S.A. Fassler, and R.E. Schmidt. 2000. Mast cell tumor in a common green iguana (*Iguana iguana*). Proc. Assoc. Reptilian Amphibian Vet. 45-46.

77. Santoro, M., B.A. Stacy, J.A. Morales, P. Gastezzi-Arias, S. Landazuli, and E.R. Jacobson. 2008. Mast cell tumour in a giant galapagos tortoise (*Geochelone nigra vicina*). J. Comp. Pathol. 138:156-159.