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SELECTED ASPECTS OF NEOPLASTIC PROGRESSION IN REPTILES

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Reptiles first appear in the Mississipian (upper Paleozoic) during the history of the earth. They are the ancestral stock of mammals and birds. The mammals appeared before the birds in the Triassic (Mesozoic) and the birds followed as the last group of vertebrates in the Jurassic (Mesozoic). Reptiles are therefore phylogenetically an important group in regard to the last diversification of the vertebrates. Neoplasms of mesozoic reptiles were described by R.L. Moodie (30).

Comparative pathology is the basis for new progress in the study of diseases of various species with different taxonomic position and the comparison of the different classes of vertebrates may shed new light on the tissue and organ susceptibility to primary or metastatic growth. Cell types from nearly every determined system in reptiles, amphibians and fish are capable of neoplastic transformation (16). Without mentioning certain papillomas in turtles and lizards (21) Jacobson counts 195 reports of neoplasms in reptiles, 28 in Chelonia (11 malignant), four in Crocodilia (1 malignant), 30 in Sauria (12 malignant) and 97 in Serpentes (68 malignant). There is no report in Rhynchocephalia (*Sephenodon punctatus*). In turtles, 17 species were involved, 3 in crocodilians, 23 in lizards, and 45 in snakes.

A look at the circulatory system in regard to neoplastic spreading is in order because the circulatory system is so important for tumor spreading (38). The separation of oxygenated and unoxygenated blood has almost been achieved in reptiles due to the anatomy of the heart exhibiting incomplete separation of the single ventricle by a septum and a division of the conus (if present) to its base to the wall of the ventricle. Separation of oxygenated and unoxygenated blood has nearly been achieved in the reptile (1). Actually, crocodilians have a true fourth-chambered heart, with moving via a foramen in the aorta. *Karge arterues* exhibit little collagenous tissue, cutaneous veins are lacking. Lymphatic vessels are well developed with thoracic ducts present and terminating into the innominate veins in the neck region. Posterior lymph hearts may be present and pump lymph into the iliacs. The spleen resembles that of mammals and birds. Lymph sinuses are scarce. It is assumed that lymph nodes first appear phylogenetically in the mesentery of crocodiles (1); but there is also much debate whether true lymph nodes are present in reptiles. The main lymphatic vessel forms a sheet around the dorsal aorta in some snakes (5).

Tumor spreading may be direct, in which case the secondary tumors invade for example a vein and continues to growth therein. The secondary tumor remains connected with the primary tumor. In distant tumor spreading known as metastasis, there is lymphohematogenous spreading, seeding on the coelomic surfaces and spreading by implantation on epithelial surfaces. R. Willis, (38), considered metastasis from teratomas as a separate type of spreading. Direct spread as of a liver cell carcinoma in the lizard *Eumeces fasciatus* and metastatic spreading of various neoplastic types in turtles, crocodiles and lizards have been observed (21). Spreading on coelomic surfaces, on epithelial surfaces, and metastasis from teratomas can be assumed to occur also; nevertheless they have not been reported. The collection of the Zoological Society of San Diego studied by Effron and Benirschke (8) revealed neoplasia of 2.19 percent of 1,233 necropsies of reptiles. Lymphosarcomas occurred with high frequency in reptiles and birds. It is noteworthy that no neoplasia were detected among 198 amphibian necropsies. Ermoschenkov and Khudoley (11) reported two tumors in 34 reptiles found among 50 neoplasms of 716 animals which had died and autopsied between 1930 and 1974 in the Leningrad Zoo.

Viruses have been found associated with neoplastic growth processes in reptiles (21). Recent findings concerning the distribution of nucleotide sequences related to cDNAsarc in viral genomes as well as cell nucleic acids are summarized by Stehelin and Roussel (35) who postulated that all upper vertebrates contain in their DNA nucleotides sequences related to cDNAsarc. The values of annealing observed, if standardized to 100% for chicken DNA, decrease to 73% for primitive birds, 38% for mammals and reptiles, 26% for fishes. The tumorigenicity of Rous sarcoma virus (RSV) was studied in 22 reptile species representing 10 families of the orders Chelonia and Squamata by Tubcheninova et al. (36). RSV did not induce tumors in 13 inoculated species. In nine species, RSV induced polymorphous sarcomas with spindle-shaped (fibroblast-like), round, and polynuclear cells. Chromosome analysis indicated that the tumors originated in the reptile cells. Tumors were induced in adult reptiles with a patent period of only 1–3 mo by inoculation with a 30% cell-free homogenate of Schmidt-Ruppin strain RSV (4 × 10**7 sarcomagenic doses per snake; 10**6–10**7 sarcomagenic doses per lizard). The case of tumor induction suggests that reptiles are more susceptible to this strain of RSV than mice, rats, guinea pigs, rabbits, and monkeys. The tumors of two snakes were tumorigenic in chickens. Since RSV is oncogenic for a wide range of birds and mammals as well as reptiles and since these three classes belong to the tetrapods the pathogenicity of RSV for these animals appears to be predetermined by evolution.

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An adenovirus-like cytopathic agent, designated frog adenovirus 1 (FAV-1) was recovered by Clark, H.F. et al. (6) from turtle (TH-1) cell cultures inoculated with cells of a granuloma-bearing kidney of a leopard frog, *Rana pipiens*. Virus replication, as indicated by cytopathic effect (including intranuclear inclusions) was limited to TH-1 cells. A variety of other cell types from amphibians, reptiles, fish, and mammals were refractory to infection. FAV-1 appears to be an 'orphan' virus, and the first described adenovirus from apoikilothermic vertebrate. It has a host range in cell culture, antigenic composition, and temperature requirement for replication that are unique among members of the adenovirus group.

Herpes-viruses are the only DNA viruses associated with lymphoid tumors, namely animal lymphosarcomas in molluscs, fish, reptiles and mammals (13).

Corticotropin-releasing factor (CRF)-containing cells have been shown to be present in the pancreas of representative species of fishes, amphibians, reptiles, birds, and mammals including man. Light and electron microscopic

Table 1. Neoplasm metastasis in reptiles.

Reptilian order	*Family*	*Species*	*Primary neoplasm*	*Metastasis with location*	*Author*	*Year*
A. Chelonia (turtles)	Pelomedusidae	*Pelusius subniger*	Carcinoma of stomach	Metastases to kidney	Cowan	1968
	Testudinidae	*Geomyda trijuga*	Carcinoma of thyroid	Metastases to mediastinum	Cowan	1968
		Emys orbicularis	Oral squamous cell carcinoma	Metastasis to liver	Billups, Harshbarger	1976
		Terrapene carolina	Adenocarcinoma of kidney	Metastases to liver	Ippen	1972
B. Crocodilia (crocodiles)	Crocodylidae	*Crocodylus porosus*	Round cell sarcoma of liver	Metastases to cerebellum and heart	Scott, Beattie	1927
C. Squamata: Sauria (lizards)	Agamidae	*Hydrosaurus amboinensis*	Malignant lymphoma (kidneys?)	Metastases all vital organs	Zwart, Harshbarger	1972
	Lacertidae	*Lacerta sicula zetti*	Malignant lymphoma, neck	Metastases to all major organs	Lawson	1962
		Lacerta sicula	Mesenchymal, sarcoma (fibrosarcoma), forleg	Metastases to mediastinum, mesentery, aorta, stomach and lungs	Elkan, Cooper Harshbarger	1976 1975
	Scincidae	*Eumeces fasciatus*	Liver cell carcinoma	Direct spread into body cavity	Ippen	1972
	Varanidae	*Varanus komodoensis*	Carcinoma of colon	Metastatic adenocarcinoma in spleen[1]	Harshbarger	1976
		Varanus exanthematicus	Leiomyosarcoma (intestine)	Metastasis to liver[1]	Harshbarger	in preparation
D. Squamata: Sepentes (snakes)	Boidae	*Eunectes murinus*	Lymphosarcoma	Diffuse metastasizing	Frank, Schepky	1969
		Python sebae	Ovarian adenocarcinoma	lung, liver, kidneys	Bland-Sutton	1885
		Python molurus	Oral carcinoma	Metastases to liver	Wilhelm, Emswiller	1977
		Python molurus	Mucinous adenocarcinoma of the liver	liver, intestine, kidney	Billup, Harshbarger (AFIP)[2]	1976
		Constrictor constrictor	Adenocarcinoma, mesentery	Cervical	Elkan, Cooper	1976
	Colobridae	*Pituophis melanoleucus*	Malignant melanoma, skin of tail	Metastases to liver	Ball	1946
		Pituophis melanoleucus	Sarcoma, (leiomyosarcoma?) abdominal	Liver, pancreas, celiac area	Cown	1968
		Matrix stolata	Hemangioendothelioma (hepatic or splenic origin)	Pulmonary, cardiac and renal metastases	Ippen	1972
		Lampropeltis getulus getulus	Lymphosarcoma	Metastasis in all major organs	Jacobson et al.	1981
		Elaphe obsoleta rossalleni	Melanoma	Local spread and metastasis via blood stream into most organ systems	Elkan	1974
		Elaphe guttata guttata	Fibrosarcoma of skin	Metastatic to liver	Harshbarger	in preparation
		Heterodon platyrhinos	Lymphosarcoma	Metastasizing to lung, kidney	Cowan	1968
	Elapidae	*Naja melanoleuca*	Carcinoma of Poison gland	Metastases to cervical region	Hill	1952
		Naja naja	Lymphosarcoma	Metastatic to heart and liver	Cowan	1968
		Naja naja	Rectal leiomyosarcoma	Metastasis to liver	Harshbarger	1974
		Naja nigricollis	Osteochondrosarcoma	Metastatic to kidney and spleen		in preparation[1]
	Viperidae	*Bitis arietans*	Adenocarcinoma	Metastasizing	AFIP[2]	
		Bitis arietans	Granulosa cell tumor	Renal metastasis	Onderka, Zwart	1978
		Bitis nasicornis	Lymphosarcoma	Metastasizing to liver, kidneys, adrenal glands, spleen, gut wall	Cowan	1968

[1] See text figures.
[2] Armed Forces Institute of Pathology, Registry of Veterinary Pathology, Washington, D.C.

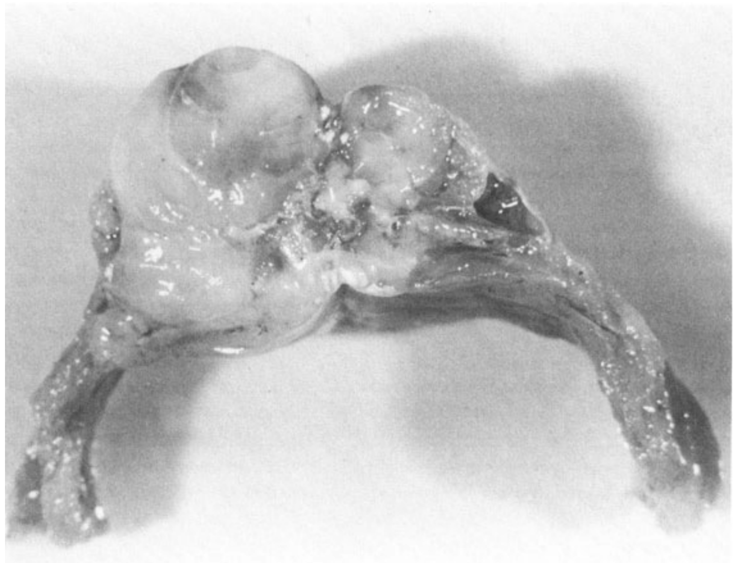


Figure 1

Figure 2

Figure 1. Osteochondrosarcoma in the spinal column of a spitting cobra, *Naja nigricollis* (RTLA 2474).

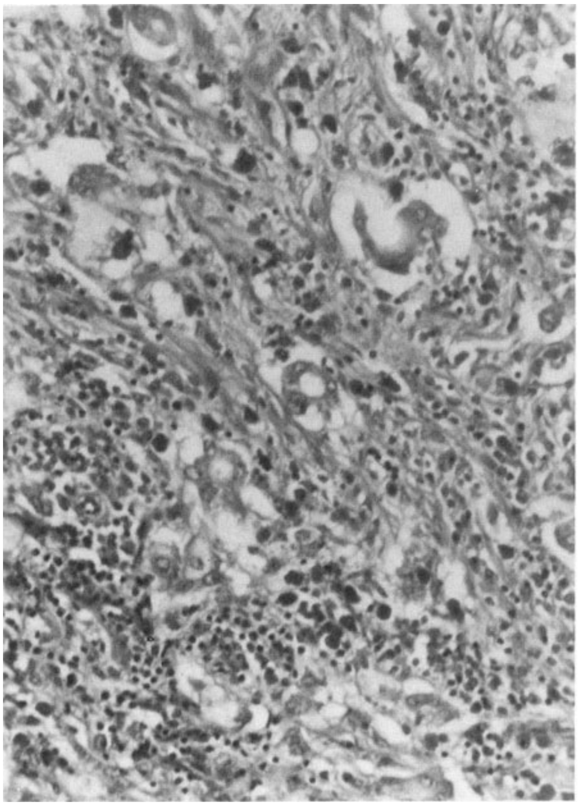
Figure 2. Kidney and spleen with metastatic osteochondrosarcoma (RTLA 2474)

Figure 3. Spleen from Komodo dragon, *Varanus komodoensis* with metastatic mucinous adenocarcinoma primary in the colon. H&E X293 (RTLA 1166).

Figure 4. Osteochondrosarcoma in the spinal column of a spitting cobra, *Naja nigricollis*. H&E X29 (RTLA 2474).

Figure 5. Higher magnification of vascular embolus of specimen above. H&E X80 (RTLA 2474)

Figure 6. Kidney with metastatic osteochondrosarcoma in interstitium (note glomeruli and tubules). H&E X47 (RTLA 2474)



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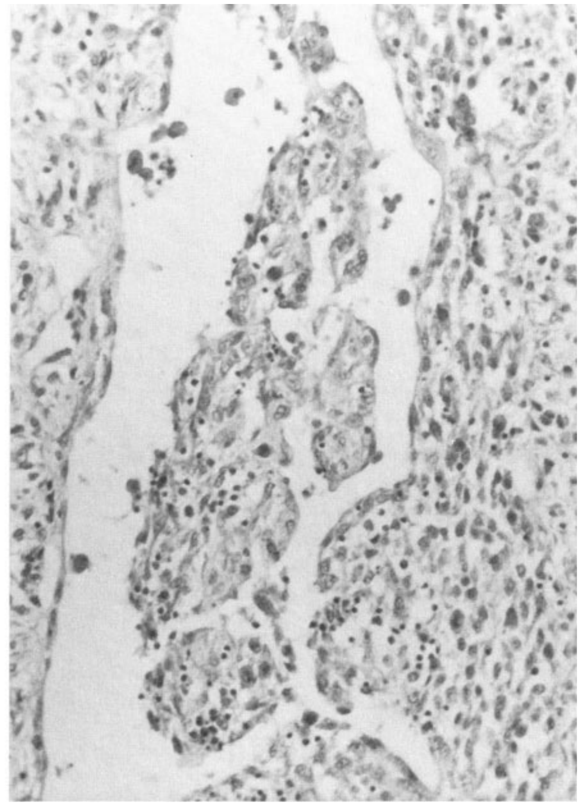

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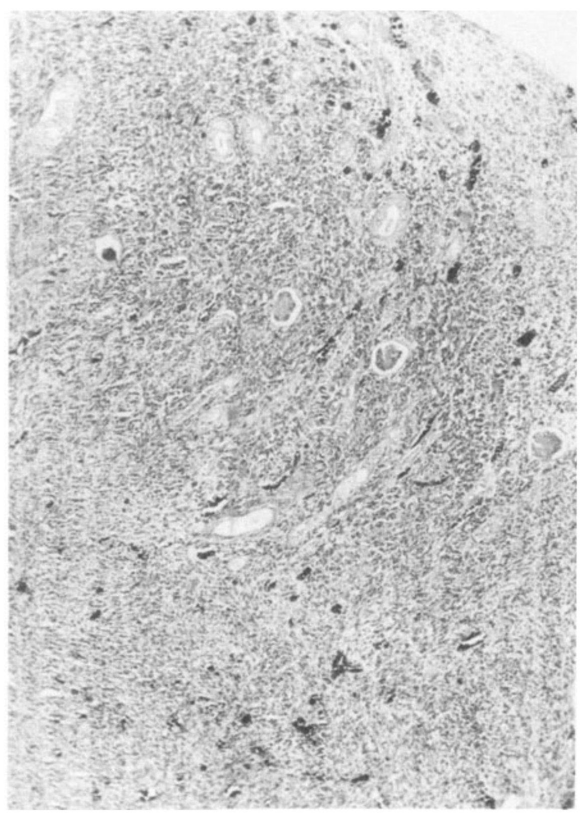

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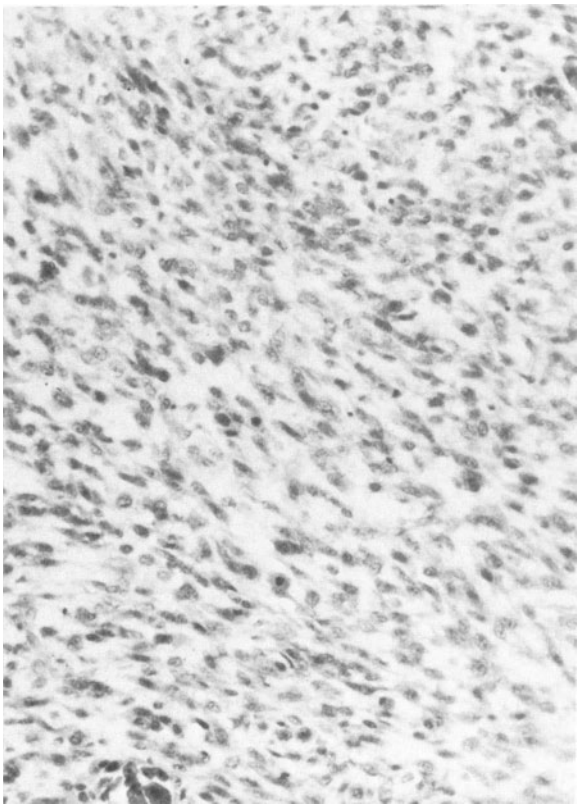

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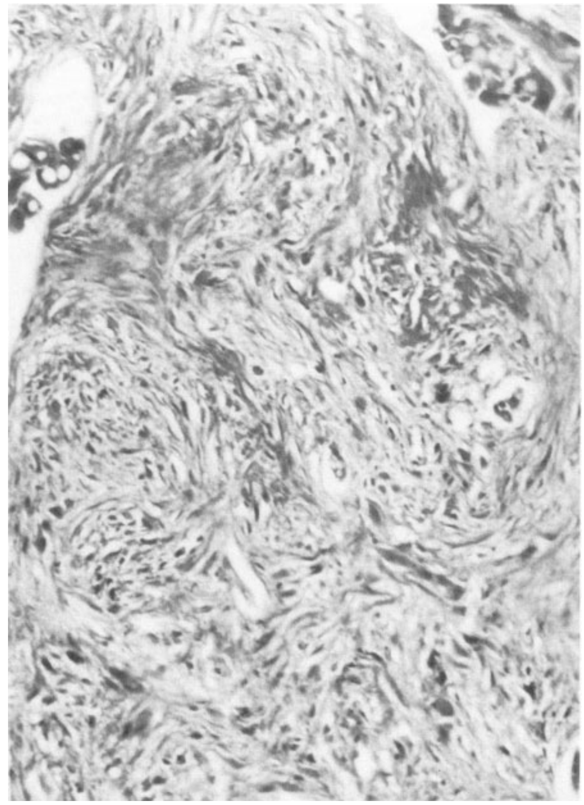

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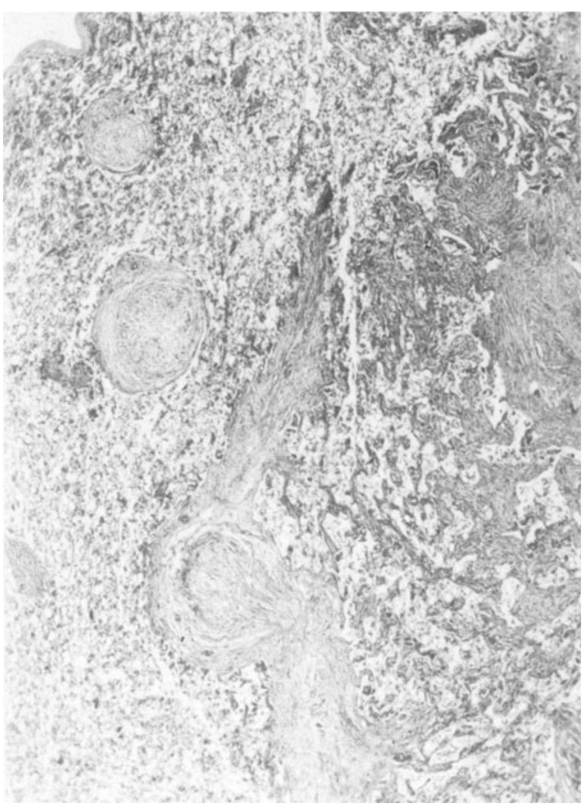
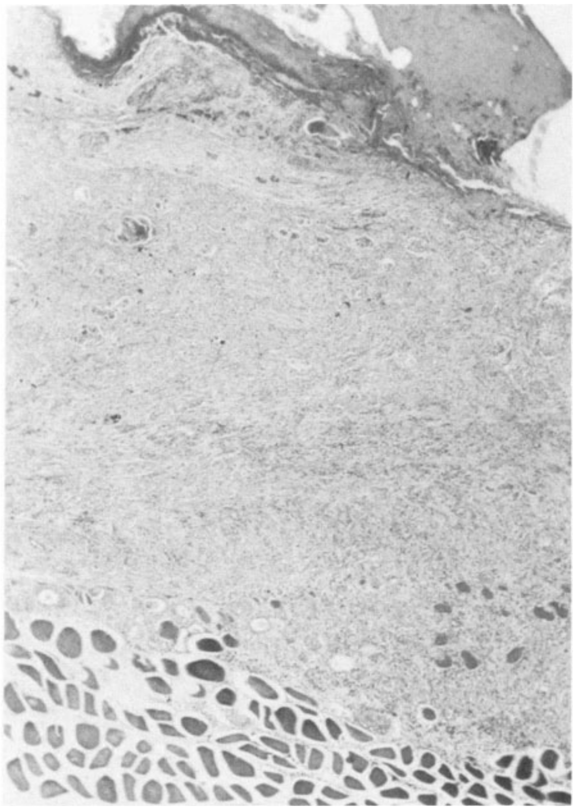


Figure 8

Figure 7. High magnification of Figure 3 demonstrating spindling and streaming of tumor cells. H&E X293 (RTLA 2474)

Figure 8. Liver containing intravascular nodules and intrasinusoidal cords/sheets of metastatic leiomyosarcoma primary in the intestine from a Savannah monitor, *Varanus exanthematicus*. H&E X47 (RTLA 2518).

Figure 9. High magnification of specimen above. H&E X293 (RTLA 2518).



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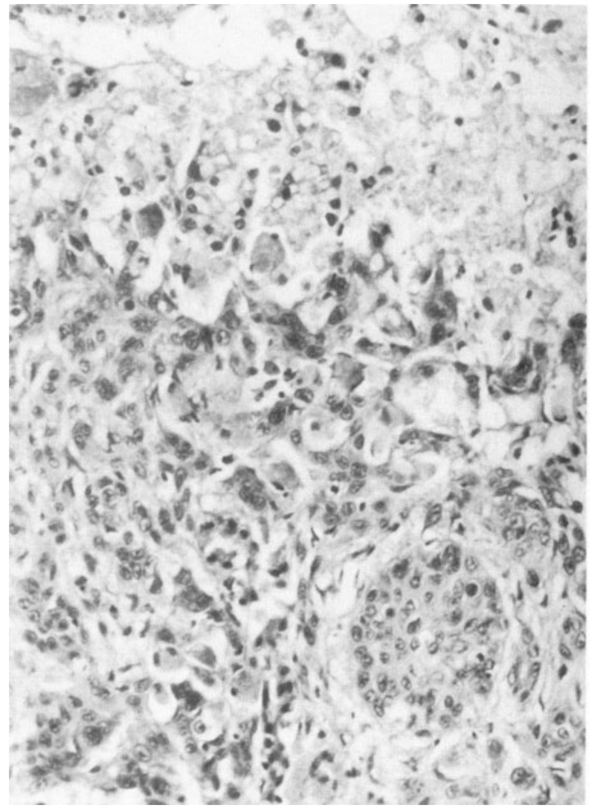

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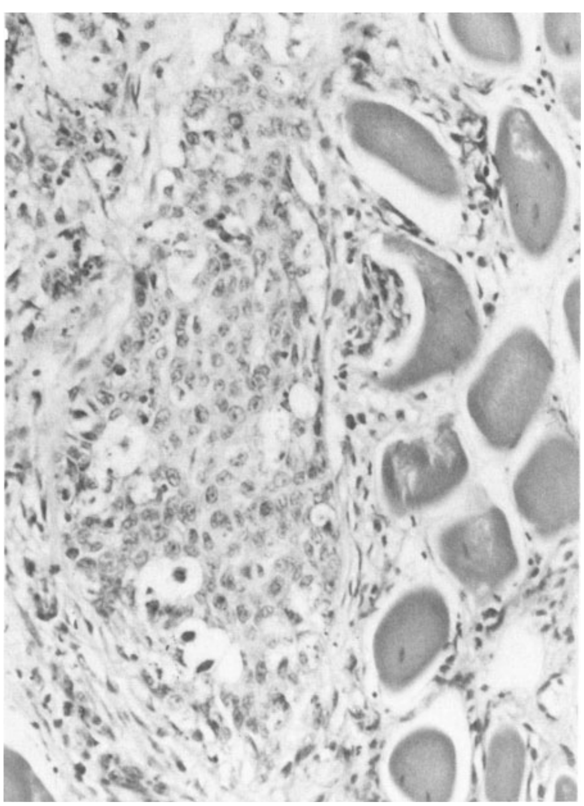
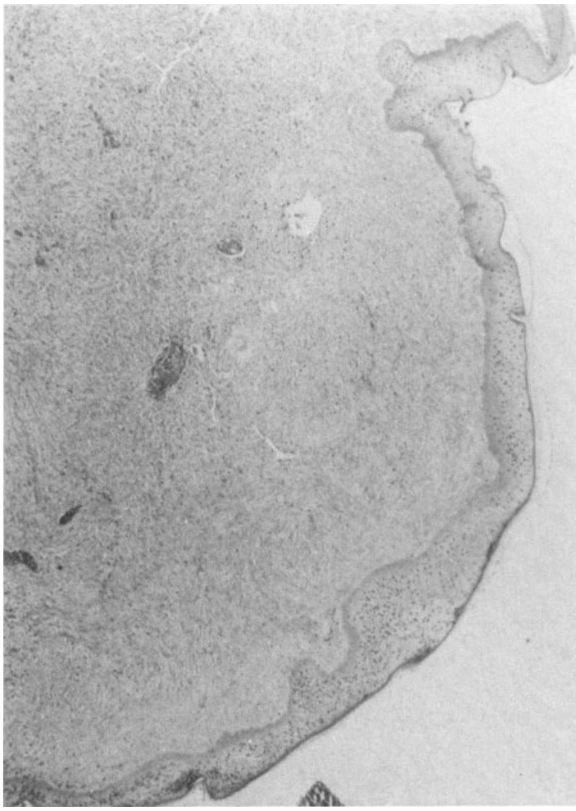


Figure 11

Figure 10. Skin from leopard geko, *Eublepharis maculatus*, with squamous cell carcinoma producing necrosis and ulceration of epidermis and extension of neoplasm through dermis with incorporation of subcutaneous muscle fibers. H&E X47 (RTLA 2774).

Figure 11. High magnification of specimen above, showing cluster of neoplastic epithelial cells, some with ballooning degeneration. H&E X293 (RTLA 2774).

Figure 12. Liver-degenerate hepatocytes (left 1/3rd of photo), vascular embolus (right corner) and sinusoidal infiltration of metastatic squamous cell carcinoma. H&E X293 (RTLA 2774).



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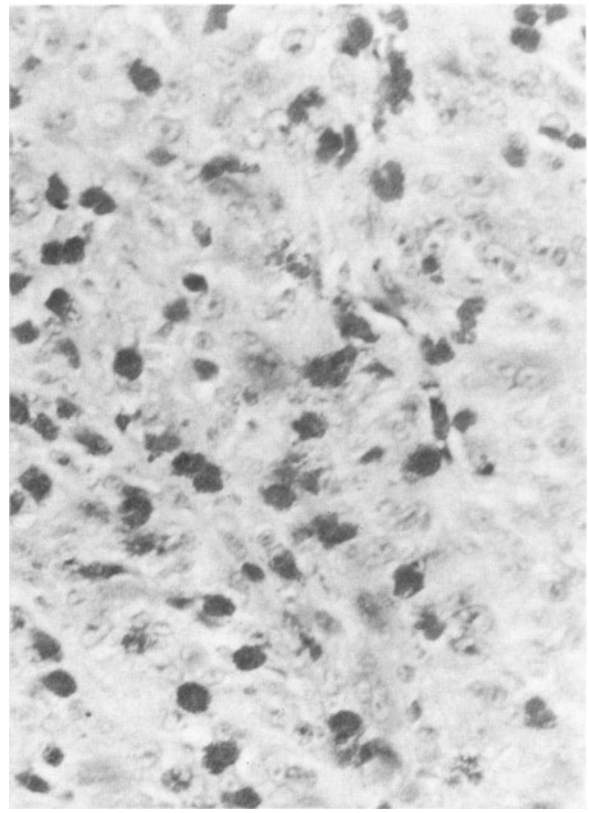

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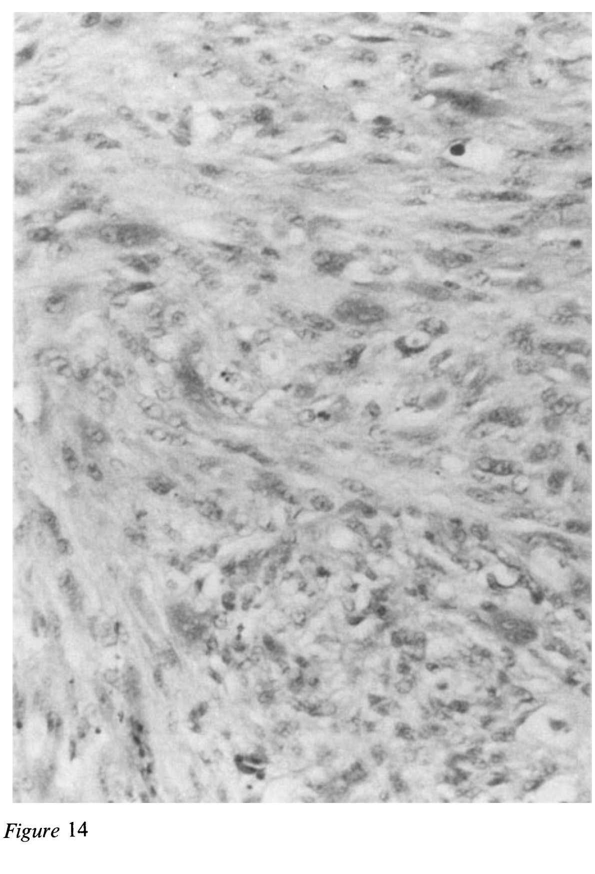

Figure 14

Figure 13. Skin from corn snake, *Elaphe guttata guttata*, containing a fibrosarcoma. Mass abuts basement membrane of epidermis but does not penetrate it. H&E X29 (RTLA 2808-1).

Figure 14. High magnification of specimen above, demonstrating packets/bundles and cords of plump, oval-to-spindle shaped nuclei. H&E X293 (RTLA 2808).

Figure 15. Higher magnification of same specimen, demonstrating numerous eosinophils within neoplasm (eosinophils are commonly numerous in reptilian skin but their presence in mammals is thought to be a significant host response to neoplasia). H&E X469 (RTLA 2808).

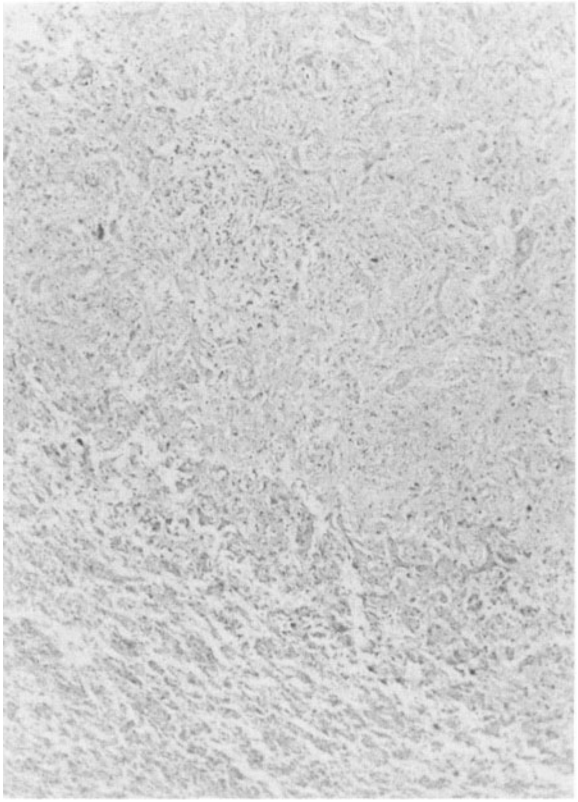

Figure 16. Liver with metastatic fibrosarcoma. H&E X47 (RTLA 2808).

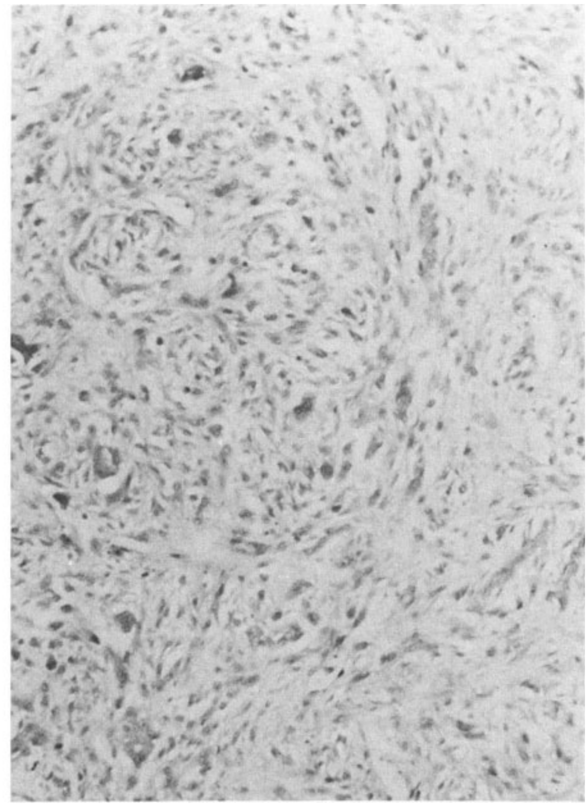

Figure 17. Higher magnification of 4 showing swirling pattern and a few trapped hepatocytes/bile duct epithelium. H&E X117 (RTLA 2808).

observations indicate that the CRF-containing cells in the endocrine pancreas are similar to glucagon (A) cells both in their morphology and distribution. Observations indicate that they are widely distributed in peripheral tissues and may represent a new tumor marker (32). Tumor markers seem to be present in reptiles as in other classes of vertebrates.

Etiology and epidemiology of cancer in mammals (primates, rodents and lagomorphs), birds, and reptiles were discussed by Kollias (27). Diagnosis and treatment of non-domestic animals will allow a more regional approach in cancer therapy in zoological medicine. The viral aspects of etiology may be important in progression/metastasis of neoplasia in reptiles.

Attempted therapy of neoplastic diseases in reptiles has included such methods as surgery and chemotherapy. The techniques of verterinary cryotherapy, for example, and its use in dogs, cats, horses, cattle, and reptiles were reviewed by Podkonjak (33).

The secondary neoplasms of reptiles found today are summarized in Table 1 followed by photographs of selected tumors demonstrating their macroscopic and/or microscopic appearance.*

*Histologic sections of the photographed neoplasms are on file at the Registry of Tumors in Lower Animals (RTLA), Smithsonian Institution, Washington, D.C. and were made available by the registries Director, John C. Harshbarger, Ph.D.

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