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Frog Decline, Frog Malformations, and a Comparison of Frog and Human Health

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The decline in frog populations and the increase in the frequency of frog malformations are discussed. Topics considered for analysis include chytridiomycosis, retinoids, UV-B radiation, chemical contaminants, environmental threats, introduced invasive species and predation, unsustainable use, and enigmatic decline. Care must be taken to distinguish between hypotheses, laboratory experiments, and the findings in feral frog populations. Clearly, the causes of population decline and malformations are heterogeneous. The subject of frogs and humans is addressed under three subheadings: the importance of frogs to human societies, medical implications of frog studies, and a comparison of frog and human disease factors. © 2001 Wiley-Liss, Inc.

KEY WORDS: chytridiomycosis; trematode infestation; limb malformations; retinoids; methoprene; pesticides; herbicides; UV-B radiation; habitat loss; acid rain; global warming; predation; unsustainable use; enigmatic decline; magainin; caerulein; neuroleptic properties of frog skin; prostaglandin E2

INTRODUCTION

This article analyzes the decline in frog populations and the increase in frequency of frog malformations. Factors affecting frog health are then compared to those affecting human health. Population decline and malformations in frogs are considered to be separate classes of problems and are commonly studied independently. Theoretically, however, overlap is possible in some instances. For example, Johnson et al. [1999] showed experimentally that exposure to the cercariae of the trematode parasite *Ribeiroia* caused severe limb malformations, and that an increase in parasite density not only increased the frequency of limb anomalies but was also associated with decreased tadpole survivorship. Furthermore, frogs with hindlimb malformations may be more susceptible as prey [e.g., see Tarrant, 1998].

Frogs are biologically diverse. They live in water and on land. They are vegetarians as tadpoles and carnivores as adult frogs. They have permeable, unprotected skin, and appear to be more sensitive to environmental change than are reptiles, birds, and mammals [Doyle, 1998; Morell, 1999b]. Thus, frog populations are very sensitive indicators of various environmental perturbations.

Some of the postulated causes of population decline and malformations are: 1) environmental pollutants, particularly biocides; 2) disease, particularly fungal; 3) parasites; 4) habitat loss and degradation; 5) global climate change; 6) introduced invasive species; and 7) unsustainable use (Table I).

CAUTIONS

Care must be taken to distinguish between hypotheses, laboratory experiments, and the findings in wild frog populations. Clearly the causes of both population decline and malformations are heterogeneous. The identification of a causal agent in a wild frog population does not preclude other causes in different frog populations. In fact, other causes are to be expected. Furthermore, two or more factors may act in concert to produce a cumulative effect. Some findings in a wild frog population may even be enigmatic, with no reasonable hypothesis being offered (see Table I). Care must be taken to analyze different frog populations separately, and the problems of other amphibians [Sessions, 1998] and reptiles should be separated in analysis as well. It is also important to establish backgrounds of frog declines and frog anomalies in different populations against which to measure the effects of various perturbations [Pechmann et al., 1991; Pechmann and Wilbur, 1994].

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TABLE I. Some Factors to Consider in Population Decline and Hindlimb Malformations in Frogs

Types of factors	References
Environmental pollution	
Metals, pesticides, herbicides, radioactive waste, ? retinoid mimics and/or breakdown products, steroid mimicking contaminants. May have direct or indirect effects. Limb anomalies experimentally produced. Acid rain; if pH drops below 4.5, frogs and other species in ponds and lakes disappear.	Bishop and Gendron [1998]; Fort et al. [1999a,b; Hall and Henry [1992]; Hayes [1997]; Kirk [1988]; Marco et al. [1999]; Ouellet et al. [1997]; Chambon [1993]
Diseases	
Chytrid fungus (*Batrachochytrium dendrobatidis*), iridoviruses (*Ranavirus*), ? suppression of immune system	Berger et al. [1998]; Longcore et al. [1999]; Pessier et al. [1999]; Cunningham et al. [1996]; Alford and Richards [1999]; Carey [1993]; Daszak et al. [1999]
Parasites	
Trematode flatworm (*Ribeiroia*); Infection in frogs by larvae (*cercariae*); use of aquatic snail host (*Planorbella tenuis*); results in hindlimb malformations	Johnson et al. [1999]
Habitat loss and degradation	
Loss of wetland acreage and clearing of forests has resulted in amphibian decline	Alford and Richards [1999]; Leja [1998]; Lannoo et al. [1994]; Welsh and Ollivier [1999]
Global climate change	
Increase in greenhouse gases and global temperature warming; could accelerate degradation of wetland acreage with further population decline in amphibians	Poiani and Johnson [1991]; Schneider and Root [1998]
Atmospheric ozone depletion, resulting in increased UV-B radiation. ? Reduced hatching success and decreased survival to metamorphosis. No direct evidence for limb malformations in the wild, but ? might act indirectly by activating photosensitive compounds or producing various breakdown products that could result in anomalies	Blaustein et al. [1994]; Stocum [2000]
Introduced invasive species	
Some frog populations reduced by introduction of bullfrogs (*Rana catesbeiana*) and non-native fish	Fisher and Shaffer [1996]; Stolzenburg [1999]
Unsustainable use	
Overcollection for food, biological supply houses, and pet trade	Dodd [1997]; Jennings and Hayes [1985]; Lannoo et al. [1994]; Oza [1990]
Enigmatic decline	
Australian gastric brooding frog (*Rheobatrachus silus*) has ceased to be found in nature	Tyler and Carter [1981]; Reaser [2000]

Thus, frog studies to date must be interpreted with caution, and it is important to not "jump" to unwarranted conclusions.

CAUSES OF POPULATION DECLINE

Chytridiomycosis

Members of the phylum Chytridiomycota are commonly found in soil and water, where they act as primary degraders or saprobes, using substrates such as plant detritus, chitin, and keratin. Other members are obligate parasites of algae, fungi, vascular plants, rotifers, nematodes, and insects [Sparrow, 1960; Karling, 1977]. Berger et al. [1998] found that chytridiomyosis caused mortality in frog populations in the rain forests of Australia and Central America. Several lipid globules and other ultrastructural defects suggested a new chytrid genus. The chytrid fungus that produces the lethal skin infection in frogs is *Batrachochytrium dendrobatidis*.

The fungal infection was found on the keratinized skin of dying and dead frogs. The infection was absent, for the most part, in tadpoles who lack keratin (only part of their mouths are keratinized). Experimental laboratory transmission of cutaneous chytridiomycosis in unaffected captive-bred Australian and Central American frogs also demonstrated chytrid infection of the frog skin, thus confirming the results of field studies [Berger et al., 1998].

The mechanism by which chytridiomycosis kills frogs is unknown. The fungus may impair cutaneous respiration and osmoregulation, or death may be caused by the absorption of toxic products released by the fungus [Berger et al., 1998]. The fungus appears to spread to previously unexposed frog populations in Australia, and travels at a rate of about 100 km per year.

Why chytridiomycosis has emerged as a disease in frogs in both Australia and Central America is problematic. There are several possibilities. First, two similar pathogens may be involved. Second, insects carrying the fungus in a moist environment, such as the gut, could glide on air currents for thousands of miles. In fact, insects are known to travel such long distances [Johnson, 1969]. Third, a single pathogen might have been introduced by researchers traveling between Australia and Central America carrying chytrid on their boots. Finally, increased virulence or increased host susceptibility may result from environmental factors or some as yet undetected co-infections [Berger et al., 1998; Kaiser, 1998; Morell, 1999a].

Environmental Threats

Habitat loss, specifically of wetlands and forests, is a serious threat to frog populations. Once, massive wetland areas were maintained by herds of buffalo, who created systems of wallow in the Great Plains, and by beavers, who built dams and created massive wetland systems throughout much of the United States; these are now gone from many regions that have become dry. The continual draining of additional wetlands and the clearing of forests for commercial purposes and for urban and suburban expansion have caused and continue to cause a decline in frog populations [Lannoo et al., 1994; Leja, 1998; Alford and Richards, 1999; Welsh and Ollivier, 1999]. An increase in greenhouse gases and global temperature warming could accelerate the degradation of wetland acreage, with a further population decline in amphibians [Poiani and Johnson, 1991; Schneider and Root, 1998].

Industrial and automobile pollution of the air with sulfur dioxide and nitric oxide causes acid rain. When the pH of lakes and ponds drops below 4.5, frogs and other species disappear [Nadakavukaren, 1995]. Blaustein et al. [1994] suggested that ozone depletion producing an increase in UV-B radiation might possibly reduce hatching success and decrease survival to metamorphosis.

Introduced Invasive Species and Predation

Frogs and other amphibians provide a prey base for birds, reptiles, mammals, spiders, and some insects. Some species of snakes and bats consume only amphibians, and some amphibians are known to consume each other [Reaser, 2000].

Many nonnative species have been introduced outside their native ranges for several reasons: 1) commercial, 2) recreational, 3) for feeding other species, and 4) to serve as biological control agents for pests. Invasive species include fish, bullfrogs (*Rana catesbeiana*), and crayfish, who compete with frogs for insect prey and who consume frog eggs, tadpoles, and adult frogs [Reaser, 2000]. This has been a serious threat to some frog populations [Fisher and Shaffer, 1996; Stolzenburg, 1999].

Enigmatic Decline

Malformed limbs (vide infra) are likely to increase the vulnerability of newly metamorphosed frogs to predation. It has been speculated that truncated limb anomalies may represent disruptive amputations. It is known experimentally that bullfrog tadpoles bred in cramped quarters prey on each other's developing limbs [Kaiser, 1997]. However, Meteyer et al. [2000] provided evidence that does not support predation as a major cause of truncated limb anomalies in frogs. In their anatomic study, no soft-tissue reactions, such as hemorrhage, inflammation, pigmentary changes, and scarring, were observed. Furthermore, frogs with amelia lacked a coxofemoral joint and 73% of them had reduced pelvic elements, strongly suggesting developmental error rather than amputation [Meteyer et al., 2000].

The Australian brooding frog (*Rheobatrachus silus*), named for its ability to swallow and brood its young in its stomach, has not been observed since 1981 and is presumed to be extinct. The frog had inhabited a relatively undisturbed tropical forest far from routine human activity. Depletion of hardwoods by forest contractors may have damaged water quality in the creeks formerly occupied by the frogs. Such damage may have included deposits of fine wood particles and an alteration in the pH. The loss of the gastric brooding frog is tragic because physiological study might have provided clues for treating human ulcers and other gastrointestinal disorders [Tyler and Carter, 1981; Tyler, 1984; Reaser, 2000] (vide infra).

Unsustainable Use

The overcollection of frogs for food, biological supply houses, and use in the pet trade can result in a decline in some frog populations [Jennings and Hayes, 1985; Oza, 1990; Lannoo et al., 1994; Dodd, 1997].

CAUSES OF LIMB MALFORMATIONS

Types of Malformations

Meteyer et al. [2000] studied limb anomalies in northern leopard frogs (*Rana pipiens*) from Minnesota, Vermont, and Maine. Of 182 frogs, 86% had hindlimb malformations. Amelia and hypogenesis were most commonly observed. Bilateral hindlimb anomalies were not encountered frequently ($n = 22$), and only a few were bilaterally asymmetrical ($n = 8$). Limb malformations were studied radiographically and dissected. They could be classified into four major categories: 1) amelia; 2) polymelia, polydactyly, and polyphalangy; 3) phocomelia, ectrodactyly, and brachymelia; and 4) bone rotations, bone bridging, micromelia, and skin bridging.

Stocum [2000] estimated a 2–3% background frequency of hindlimb malformations partially attributable to genetic mutations. Malformed frogs have been observed for at least 250 years. The background frequencies of malformations in many frog populations are still not known [Kaiser, 1997; Tarrant, 1998]; it is important to establish backgrounds of frog anomalies in different populations against which to measure increased frequencies.

Meteyer et al. [2000] found that malformations of a given type tended to occur in frogs collected from the same site, but the types of anomalies differed widely in dispersed populations. Limb malformations of such variety strongly suggest etiologic heterogeneity. No one genetic or environmental factor can explain the diversity of anomalies found in natural frog populations. Factors studied to date have included parasites, retinoids, chemical exposure, UV-B radiation, and predation [Sessions and Ruth, 1990; Ankley et al., 1998; Fort et al., 1999a, b; Gardiner and Hoppe, 1999; Johnson et al., 1999; Sessions et al., 1999; Burkhart et al., 2000].

Trematode Infestation

Johnson et al. [1999] reported multileggedness and other hindlimb malformations in ponds that support California tree frogs. The ponds contained aquatic snails (*Planorbella tenuis*), the first host of the trematode parasite *Ribeiroia*. Dissection of abnormal frogs showed a unique distribution of trematode cysts (metacariae) in the pelvic girdle and hindlimbs.

Johnson et al. [1999] showed that severe limb malformations could be induced in Pacific tree frogs (*Hyla regilla*) by exposure to the cercariae of the trematode parasite *Ribeiroia* (Table II). An increase in parasite density increased the malformation frequency, and was also associated with decreased tadpole survivorship. The malformations were very similar to those observed at wild field sites where the parasite was found. However, multilegged frogs above background levels may also be found in trematode-free sites [Stocum, 2000], indicating etiologic heterogeneity.

How trematode parasites interfere with hindlimb development is unknown, but probably chemical and/or physical disturbances act on the developing limb bud. Sessions and Ruth [1990] showed that trematode cysts could be mimicked by inserting tiny plastic beads in the limb field of *Xenopus*, producing multiple limb malformations.

More than 250 trematode species are known which can burrow into developing tadpoles [Meteyer et al., 2000]. Whether species other than those of the *Ribeiroia* genus can produce polymelia is unknown. *Alaria* cysts are widely distributed subcutaneously in frogs but do not cause limb malformations because they are not concentrated in the pelvic girdle and hindlimbs [Johnson et al., 1999; Stocum, 2000].

Retinoids

Retinoids are potent human teratogens [Lammer et al., 1985], and various types of limb malformations have been experimentally induced in amphibians and other species [Chambon, 1993]. In regenerating anuran limbs, multiple limbs are induced which are *duplicated* in the proximal-distal axis [Niazi, 1996; Maden, 1998]. In contrast, retinoids *inhibit* anuran hindlimb bud development, causing reduced limbs [Niazi, 1996]. In retinoid-treated regenerating urodele limbs, the major anomaly observed is serial duplication along the proximal-distal axis. Mirror-image duplications in the anterior-posterior axis are seen much less commonly [Bryant and Gardiner, 1992].

Methoprene is a juvenile hormonal and retinoid analog that acts to retain the juvenile characteristics of insects during growth, thus preventing metamorphosis into the adult form. It also has ovicidal properties in some insects. Methoprene and its derivatives are used in a variety of agricultural and domestic pesticide products. As a retinoid mimic, it can function as a ligand for the retinoid X receptor (RXR). In high doses, it is teratogenic in mice and can result in limb malformations similar to those produced by retinoids [Harmon et al., 1995].

Ankley et al. [1998] treated *Rana pipiens* embryos with methoprene, producing craniofacial and axial defects. UV-B radiation breaks methoprene into compounds that mimic the structure and receptor binding properties of 9-cis, 13-cis, and all trans-retinoic acids. A trace amount of one of these breakdown products was identified in the water at three sites in Vermont known to harbor malformed frogs. However, levels were much lower than those required to induce malformations in the laboratory [La Clair et al., 1998].

Sessions et al. [1999] studied multilegged malformations in Pacific treefrogs (*Hyla regilla*) (Table III). Not a single example of a proximal-distal duplication was observed, nor were any found in the study of Meteyer et al. [2000] in northern leopard frogs (*Rana pipiens*). Sessions et al. [1999] concluded that the types of anomalies found in wild Pacific treefrogs were not

TABLE II. Anomalies Produced in Pacific Treefrogs (*Hyla regilla*) by Experimental Exposure to Cercariae of Trematode Parasite (*Ribeiroia*)*

Exposure	16 cercariae	32 cercariae	48 cercariae
Type of anomaly			
Forelimb	(%)	(%)	(%)
Hemimelia, ectromelia	0	0	0
Ectrodactyly	0	0	0
Cutaneous syndactyly	0	0	0
Polydactyly	0	0	0
Polymelia	0	0	0
Other	0	0	0
Hindlimb	(%)	(%)	(%)
Hemimelia, ectromelia	11.8	18.6	25.5
Ectrodactyly	0	0	2.1
Cutaneous syndactyly	17.6	9.3	12.8
Polydactyly	2.9	6.9	0
Polymelia	32.3	44.2	55.3
Digit-like appendage arising from femur	11.7	2.3	2.1
Other	23.5	18.6	2.1
Total number affected/total number treated	22/31	17/18	18/18

*Modified from Johnson et al. [1999].

TABLE III. Limb Duplications Observed in Multilegged Treefrogs (*Hyla regilla*)*

Geographical area	n	Anterior mirror image duplication	Posterior mirror image duplication	Mirror image triplication	Proximal-distal duplication
California					
Locality 1	314	41	59	24	0
Oregon					
Locality 2	2	0	2	0	0
Locality 3	12	4	5	1	0
Locality 4	2	0	2	0	0
Locality 5	7	1	1	0	0
Locality 6	52	8	11	7	0
Locality 7	1	1	0	0	0
Locality 8	1	0	1	0	0

*Modified from Sessions et al. [1999].

consistent with those induced by retinoids in experimental studies, but are consistent with trematode infestation. However, signaling during development is complex; disruption of cellular communication involving retinoic acid and related pathways may still be possible, and should not be excluded as a potential factor in limb anomalies.

UV-B Radiation

Depletion of the ozone layer has been held responsible for an increase in UV-B radiation reaching the earth. It has been suggested that such an increase has contributed to a higher incidence of melanoma and other skin cancers than is usually found at "baseline" levels in humans [Nadakavukaren, 1995], but there is no direct evidence that feral frog populations have been affected [Stocum, 2000]. However, laboratory experiments have shown that continuous exposure of developing frog embryos to UV-B radiation results, for the most part, in bilateral, blunt-ended truncations [Ankley et al., 1998]. Such malformations occurred when northern leopard frogs were exposed to about 30% of UV-B levels for at least 24 days [Kaiser, 1997]. In contrast, in wild frog populations, limb abnormalities are usually of the unilateral and tapering type rather than of the bilateral and blunted type [Gardiner and Hoppe, 1999]. Furthermore, amphibian eggs are protected by their natural pigment, as well as by the shade provided by pond vegetation and trees [Stocum, 2000]. The depth of the water is also an important factor in blocking UV-B. The effect of UV-B radiation on methoprene has already been discussed (vide supra).

Chemical Contaminants

Many chemical contaminants pollute the environment, and the wetland habitat of frogs is a repository for many toxic substances. Because frogs have porous skins, they are particulary vulnerable to chemical contamination. Agents include pesticides, herbicides, steroid-mimicking contaminants, gasoline, oil, ice-melting agents, metals, and radioactive wastes, among others. They may have direct or indirect effects. Numerous studies of various types have been carried out [Hall and Henry, 1992; Chambon, 1993; Hayes, 1997; Ouellet et al., 1997; Bishop and Gendron, 1998; Kirk, 1988; Fort et al., 1999a, b; Marco et al., 1999; Reaser, 2000]. Ouellet et al. [1997] correlated the use of pesticides with a high frequency of hindlimb anomalies in *newly metamorphosed* frogs from the St. Lawrence River Valley in Quebec. The limb-reduction defects were not observed in *adult* frogs, indicating decreased fitness.

FROGS AND HUMANS

Importance for Human Societies

Frogs serve important functions for human societies. In tropical areas, their dietary intake of mosquitoes can help in the control of malaria. In some developing countries, frogs are an important source of animal protein consumed by local people. Scientifically, embryologic processes and genomic structures are highly conserved in vertebrates; thus, research on frogs has had and continues to have far-reaching implications.

Medical Implications

The dermal glands in the skin of the African clawed frog *Xenopus laevis* secrete many peptides, including thyrotropin-releasing hormone; caerulein, a potent structural analog of cholecystokinin octapeptide; xenopsin, a structural analog of neurotensin; magainin-1 and magainin-2, potent antimicrobial agents; and an assortment of peptide precursor fragments. Also found are biogenic amines: 5-hydroxytryptamine, serotonin, and bufotenidine, a quaternary methylammonium base of 5-hydroxytryptamine [Barthalmus, 1994].

The medical knowledge derived from the study of frog skin is staggering. Skin compounds secreted by *Xenopus laevis* have been shown to be implicated in schizophrenia, Parkinson disease, animal satiety, antipsychotic drug-induced movement disorders (tardive dyskinesia, dystonia, and extrapyramidal side effects), bulemia, anorexia nervosa, hyperprolactinemia, dopaminergic and serotonergic activities, neuronal co-existence of multiple neurotransmitters, antihemorrhagic shock, animal aggression, vagus nerve function, taste aversion, hypertension, antimicrobial activity,

and control of various digestive processes [Barthalmus, 1994].

In 1987, Zasloff discovered that when the skin of *Xenopus laevis* was injured or attacked by microbes, the skin secreted copious amounts of an antimicrobial agent. He isolated two peptides that were shown to be effective in killing fungi, protozoans, and gram positive bacteria. Zasloff [1987] named the newly found antibiotics "magainins" after the Hebrew word for "shield." Magainins and their analogs have also been shown to have antitumor activity in vitro against small cell carcinoma of the lung, and the ability to rapidly lyse

TABLE IV. Comparison of Human and Frog Pathology by Various Categories

Humans	Frogs	Reference
Genetic variation, disease susceptibility, and disease protection		
CYP1A1 gene: 10% of population with CYP1A1 isoform have a seven-fold risk of lung cancer among smokers compared to those smokers with the common CYP1A1 variant	Genetic variation undoubtedly plays a role in the susceptibility of certain frog populations to disease but little is known about this	Carey [2000]; Rutherford [2000]; Weatherall [1996]
Heterozygous mutations in α and β thalassemia, hemoglobin S, C, and E, and glucose-6-phosphate dehydrogenase deficiency confer protection against malaria		
Diminished immune response		
AIDS	?Chytridiomycosis	Carey et al. [1999]; Carey [2000]
Severe combined immunodeficiency	(inflammatory response in skin is absent)	
	?Ranavirus	
Genetically caused limb malformations		
Many known causes for various types of limb anomalies	Implied causes for some limb anomalies but not proven	Cohen [2001]
Epidemics		
Bubonic plague	Chytridiomycosis	Carey [2000]
Smallpox		
New diseases and pathogens		
HIV	? New chytrid variant	Carey [2000]; Colwell and Patz [1998]; Levins et al. [1994]
Hantavirus	? Novel ranavirus	
Ebola virus	? Other	
Environmental disruption		
Disrupted soil for landscaping, construction, and agriculture in the Southwest has released arthroconidia of *Coccidioides immitis* into the air, resulting in a dramatic increase in pulmonary Valley Fever	Drainage of wetlands for human use has led decline in frog populations	Alford and Richards [1999]; Kirkland and Fierer [1996]
Herbicides and pesticides		
Dioxin, an unwanted by-product in the production of certain herbicides, can result in chloracne	Pesticides have resulted in frog population decline and in hypoplastic malformations of the hindlimbs	Netting [2000]; Ouellet et al. [1997]; Nadakavukaren [1995]
Acid rain		
Mobilization of toxic metals by acidified water has led to bioaccumulation in fish which makes them dangerous to eat. Such water is also unsafe for drinking. The causes, industrial and automotive SO_2 and NO_2, also pollute the air	When pH of lakes drops below 4.5, frogs and other species disappear	Nadakavukaren [1995]
UV-B radiation		
Skin cancer	? Reduced immunity	Nadakavukaren [1995]; Stocum [2000]
Cataracts	? Activate photosensitive compounds or production of breakdown products of methoprene. Continuous laboratory exposure of frog embryos to UV-B results in limb truncations. UV-B does not cause limb malformations in wild frog populations, but might act indirectly in the field	
Reduced immunity		
Photosensitivity		
Global warming		
Change in mosquito vectors, putting many different populations at risk for malaria	Degradation of wetland acreage results in frog population decline	Colwell [1996]; Gibbons et al. [2000]
Mobility for escaping compromised habitats and protection from environmental forces		
Great mobility and good protection against the elements	Limited mobility and limited protection against the elements	Gibbons et al. [2000]

hematopoietic cells and solid tumor cells. Finally, magainins have been reported to disrupt the sporogenic stage of malarial parasites in anopheles mosquitoes [Barthalmus, 1994].

Caerulein is a decapeptide that was first isolated from skin extracts of the Australian hylid frog *Litoria caerulea*, and later from the African clawed frog *Xenopus laevis* and the South American frog *Leptodactylus labyrinthicus*. Other members of the caerulein family have been found in several other species of frogs. Caerulein possesses antinociceptive and sedative properties. In comparing the central effects of caerulein with those of diazepam and haloperidol, the amphibian decapeptide was more potent than the other two drugs. Caerulein has been shown to relieve the pain of biliary colic and peripheral vascular insufficiency and also to relieve postoperative pain and even pain from cancer [Erspamer, 1994].

Experimental trials with predatory snakes have shown that when *Xenopus laevis* is captured by a snake, the frog's skin secretes a substance that induces oral dyskinesia, which aids in the frog's escape. The highly stereotyped orofacial movements induced in frog-eating snakes are similar to those induced in humans by antipsychotic (neuroleptic) drugs. Neuroleptic properties are found in several frog skin peptides and in one of its two indoleamines, e.g., TRH, CRL, and XN, the latter two being the analogs of cholecystokinin-octapeptide (CCK-8) and neurotensin (NT), respectively [Barthalmus, 1994].

The now extinct female gastric brooding frog (*Rheobatrachus silus*) was able to swallow and brood its young in its stomach by converting the stomach to a "uterus," later giving birth orally. The dilated stomach showed attenuated oxyntic cells with few surface projections, sparse tubulovesicular reticulum, and few pepsinogen granules and mitochondria [Tyler and Carter, 1981; Fanning et al., 1982; Tyler, 1984]. To successfully brood its young, gastric acid secretion had to be suppressed. Tyler et al. [1983] identified prostaglandin E2 as the cause, and it was probably secreted by the eggs, tadpoles, and young froglets. As already mentioned (see Enigmatic Decline section), its extinction is extremely unfortunate because physiological study might have provided information for treating human ulcers and other gastrointestinal disorders.

Frog and Human Disease Factors

It is possible to compare various frog disease factors with human disease factors. In Table IV, comparative categories include genetic variation, disease susceptibility, and disease protection; diminished immune response; genetically-caused limb malformations; epidemics; new diseases and pathogens; environmental disruption; herbicides and pesticides; acid rain; UV-B radiation; global warming; and mobility for escaping compromised habitats, and protection from environmental forces.

Although all categories of pathology in Table IV contain factors that affect both frogs and humans, the factors themselves differ in their specificity for frogs vs. humans. There are three reasons for this. First, frogs and humans are separated by a wide evolutionary gulf. Second, frogs and humans occupy different ecological niches. Third, much more is known about human pathology than frog pathology. For example, the immune system is known to play an important role in disease, and although the human immune system is well understood, the immune defenses of amphibians are well documented in only a very few species [Carey, 2000].

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