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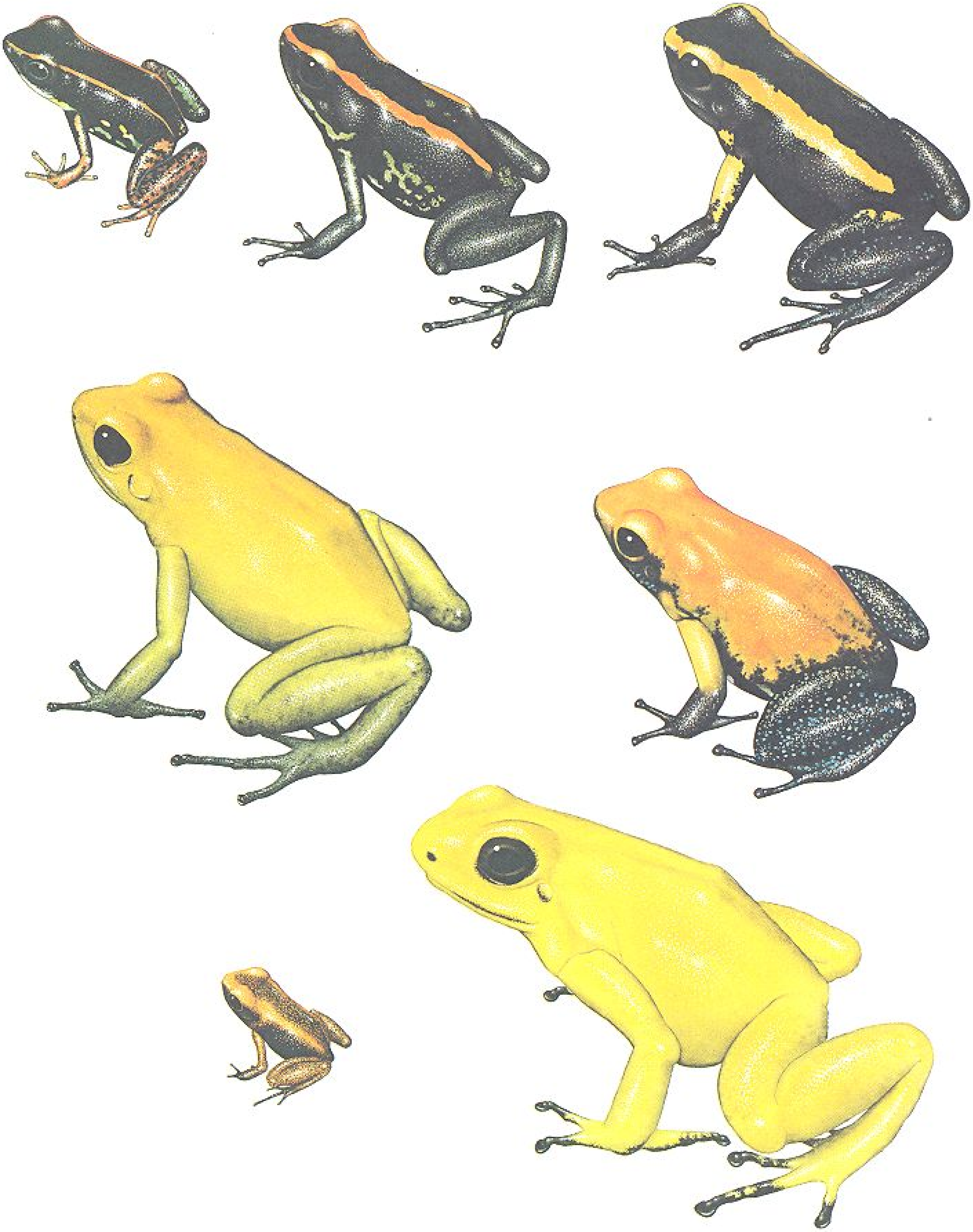


POISONOUS FROGS of the genus *Phyllobates* are shown 1.7 times life size in these paintings by David M. Dennis. The first two frogs at the top, from the left, are *P. lugubris* and *P. vittatus,* two Central American species that secrete relatively small amounts of toxins from glands in their skin. The striped frog at the upper right is *P. aurotaenia,* one of three Colombian species used for poisoning blowgun darts. In the middle row are two specimens of *P. bicolor,* the second of the three Colombian species. They show extremes in size and color variation; the legs, of a hue different from the body, vary from pale green to black. At the bottom is the third and most poisonous Colombian species, *P. terribilis.* The immature *P. terribilis* (*left*) is striped like its relatives at the top, but its stripes are being obliterated by the spread of bright pigment. The adult *P. terribilis* (*right*) may be yellow, orange or pale green, but normally it is uniformly colored above and below. *P. terribilis* is a bolder, less secretive frog than the other species and is at least 20 times as toxic. It is potentially dangerous even to handle.

Dart-Poison Frogs

In Colombia, Indian hunters poison blowgun darts with highly toxic alkaloids secreted by small frogs. Both the alkaloids and the evolutionary biology of the frogs raise interesting questions

by Charles W. Myers and John W. Daly

Poisonous organisms are so numerous that chemists and pharmacologists are still many years away from analyzing all the noxious molecules found in various microorganisms, plants and animals. Basic research in this area is of interest to the broader fields of ecology and evolutionary biology; it may also lead to new drugs or other useful substances. Some particularly intriguing subjects for investigation are provided by the richness of life in tropical regions. An example in the New World Tropics is the plant genus *Strychnos,* a source of the poison strychnine and of the curare alkaloids. Curare is used by Indian hunters for poisoning arrows and blowgun darts and by anesthesiologists as a muscle relaxant. Another example is provided by a family of frogs, certain species of which secrete one of the strongest animal poisons known. This substance too is used as a dart poison and has found a place in biomedical research. Other species in the same family secrete many additional toxins, and the frogs themselves are also remarkable in several aspects of their biology.

The poisonous frogs and their nontoxic relatives belong to the family Dendrobatidae, which is confined to South America and southern Central America. They occupy a wide range of habitats. Some species are found along streams; others live away from water, on or near the ground in lowland or montane rain forest. A few forest species even spend most of their lives up in the trees. At the other extreme are a few species that live in open dry country, where they find sufficient humidity on shaded ground under low vegetation. In spite of this ecological diversity the dendrobatid frogs share a life style that sets them apart from virtually all other frogs. They are active only in the daytime, and they lay their eggs in moist places on land. They tend their eggs until hatching, when a "nurse" frog carries the tadpoles, literally glued to its back, to a suitable aquatic environment.

The dendrobatid family includes more than 100 species, currently divided among four genera. They are small frogs, varying in head-and-body length from little more than a centimeter to about five centimeters. Whereas among most frogs the male is smaller than the female, in many populations of dendrobatids the male is about as large as the female. Large males are associated with a high degree of territoriality and aggressiveness. The males of such species invest much time and energy in advertising their territory and attracting mates by prolonged calling, and in actively challenging and grappling with other males. Many territorial males are noisy little creatures; their insectlike chirps, peeps or trills contribute noticeably to the daytime sounds of some tropical forests. The sight of two miniature frogs wrestling on a leaf, chirping vigorously at each other, can be amusing to a human observer, but sexual fitness and successful breeding are evolutionarily serious matters. In some species of dendrobatids the female is also aggressive and defends a territory.

The relatively large size of male dendrobatids is also associated with unusual kinds of mating behavior. Among most frogs courtship concludes with the male mounting the larger female and clasping his mate either behind her forelegs or in front of her hind legs. Male dendrobatids clasp the female not around her trunk but around her head, with the backs of the fingers pressed up under the female's chin. This forward position better ensures the fertilization of the eggs being extruded by the female; if a male of similar size were farther to the rear, its sperm could fall to the ground. In some species of dendrobatids clasping is absent from the courtship ritual, and the eggs are fertilized in the course of rather complicated maneuvering by both the female and the male.

Depending on the species, dendrobatid eggs are laid in leaf litter, in crevices under rocks, on shaded leaves aboveground or in such tropical forest growths as bromeliads and arums. The size of the egg clutch is small compared with the hundreds or even thousands of eggs laid by many water-breeding frogs; it can be as few as one or two eggs among the smallest dendrobatids and is rarely more than 30 or 40. In many dendrobatid populations a small clutch size is partially offset by the fact that breeding is continuous throughout the year. Some individual frogs can breed every month. Statistics on this point are provided by observations of a pair of frogs of the species *Dendrobates tricolor* kept at the American Museum of Natural History for more than two years. These frogs mated from two to four times a month. Clutches were produced every 10th day on the average and consisted of from 12 to 30 eggs. Even with this prodigious effort the female laid only about 600 eggs each year.

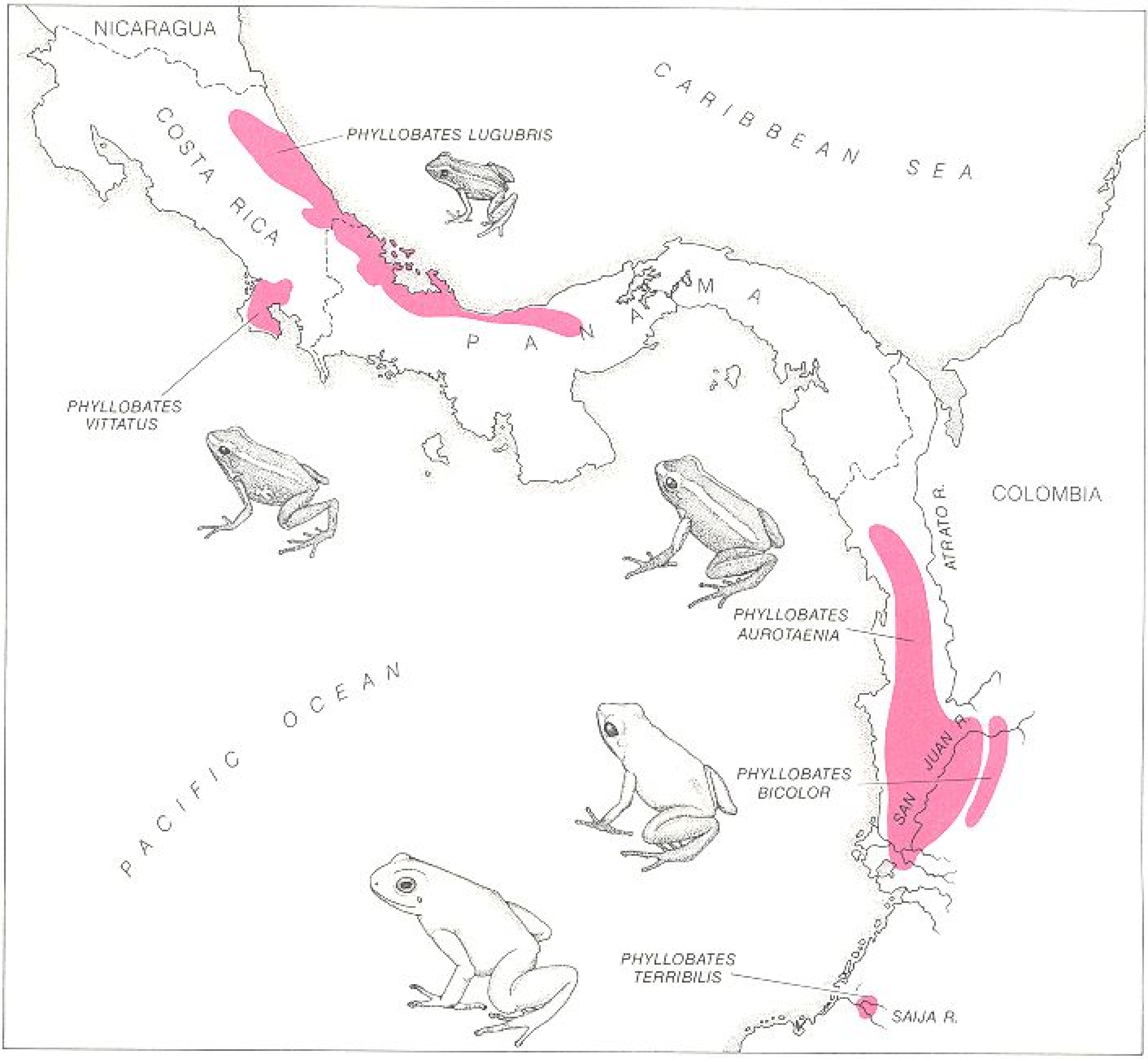
Once they are deposited the eggs may be "guarded" by either parent or may be left alone except for periodic brief visits. On such a visit the frog may moisten the eggs, apparently with water from its bladder. The nurse frog occasionally wriggles its hindquarters into the egg mass, an action that ultimately aids the hatching process and helps the tadpoles to squirm up onto their parent's back. There they adhere to a patch of mucus secreted by glands in the frog's skin. Adhesion is facilitated by the flat or slightly concave belly that is characteristic of dendrobatid tadpoles. In some species the attachment is no more than superficial; in others the mucus is gluelike and the tadpoles are firmly fixed to the adult's back. Again depending on the species, the tadpoles may remain attached to the nurse frog for an interval ranging from a few hours to more than a week. In this period the tadpoles may grow to some extent by absorbing yolk reserves.

The nurse frog eventually travels to a suitable body of water, where a period of soaking loosens the mucous bond and the tadpoles swim free. Many dendrobatids take their tadpoles to small streams. Other species release them in the small pools of rainwater that collect in bromeliads or between the leaf and the stem of certain other tropical plants. The nurse frogs of one species, *Dendrobates auratus,* often release their tadpoles in water retained by hollows in tree trunks. The tadpoles of *D. auratus* tend to resort to cannibalism in this nutrient-poor environment, and only one of them may survive to maturity.

Rainwater in small bromeliads and in the axils of leaves also seems to hold few nutrients, a circumstance that helps to explain a surprising observation made recently by Peter Weygoldt at the University of Freiburg in West Germany. Working with laboratory specimens of *Dendrobates pumilio,* a species that releases its tadpoles in such places, Weygoldt found that the females regularly visit their free-living tadpoles to deposit unfertilized eggs in the water. The tadpoles then feed on the eggs!

Biologists sometimes attempt to determine the relative "cost" of parental care by male or female animals, because such care may impose limitations on reproduction or may expose the parent to predation. These are factors to be weighed against the benefit of ensuring success for one or a few sets of eggs or for sperm from an individual parent. Among dendrobatid frogs the reproductive cost may be higher in species (such as *D. pumilio*) where the nurse frogs are usually females than it is in species where the nurse frogs are usually males. Of the *D. tricolor* pair at the American Museum the male was able to care for several clutches of eggs at a time. Furthermore, it vocalized frequently and presumably would have mated with other females if they had been available. It fed even while it was carrying on its back a full load of tadpoles, which were released into the water within hours of hatching.

It has been supposed that the sex of the nurse frog (male in most species and females in some) is a species-specific trait. In a few species, however, both sexes have been found carrying tadpoles, a fact that is hard to explain. How can such a novel behavioral trait be so variable? Experiments with the *D. tricolor* pair suggest that the answer may involve the outcome of sexual competition for the nurse role. The female of the pair was both able and willing to



DISTRIBUTION OF THE FIVE SPECIES of the dendrobatid genus *Phyllobates* is patchy. The three species found in western Colombia are the only frogs of any kind known to be used by Indian hunters for poisoning blowgun darts. The two species found in Costa Rica and Panama secrete small amounts of the same toxins as their Colombian relatives, but they do not inhabit the areas where blowguns are used.

be the responsible parent but was kept from the role by the territorial aggressiveness of the male. The female stayed with her clutch of eggs for the first hour or so; thereafter she was apparently allowed no further visitation rights. If, however, the male was removed after breeding, the female cared for the eggs and eventually carried the tadpoles as well. If the male was not removed until a few days later, the female showed no reluctance to cannibalize either her eggs or her tadpoles as though they belonged to another female. Such cannibalism may be a mechanism by which population density is regulated in some species of dendrobatids.

Much remains to be learned not only about the natural history of dendrobatids but also about their evolutionary relations and classification. The approximately 130 species are currently placed in four genera: *Atopophrynus, Colostethus, Dendrobates* and *Phyllobates*. *Atopophrynus* has only one species. *Colostethus* has more than 70, mainly brown in color. With a few exceptions these species are nontoxic. Most of the approximately 50 species of *Dendrobates* and the five species of *Phyllobates* are characterized by bright "warning" coloration. The brilliance of these frogs advertises the presence of poisonous or at least distasteful skin secretions that are effective in deterring many potential predators. Toxic dendrobatids are not, however, completely immune from predation; for example, they are preyed on successfully by large spiders and certain snakes. The frogs' secretions are released from microscopic glands in the skin at times of stress, and a predator that has seized a frog in its mouth will experience sensations of burning, numbing or foul taste that tend to make it drop the prey.

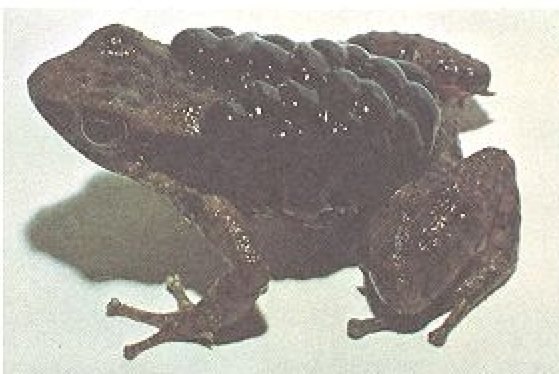
The most toxic dendrobatids are three species of *Phyllobates* from west of the Andes in the Pacific drainage of Colombia. These frogs secrete a poison that is much stronger than curare. Just as curare is a widely used poison for arrows and blowgun darts east of the Andes, so these dendrobatid toxins serve as dart poisons in western Colombia. Possibly the earliest report of their use is one written by Captain Charles Stuart Cochrane, who explored in Colombia in 1823–24 while he was on leave from the British navy.

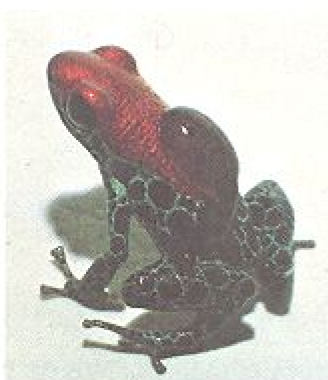
CARE OF THE YOUNG by the male or female parent includes attention to the eggs. Here a male *Dendrobates silverstonei* watches over a clutch deposited on a leaf on the forest floor.

Cochrane, crossing the western Andes on foot, had his attention drawn to frogs "called *rana de veneno* [by the Spanish], about three inches long, yellow on the back, with very large black eyes." "Those who use [their] poison catch the frogs in the woods, and confine them in a hollow cane, where they regularly feed them until they want the poison, when they take one of the unfortunate reptiles and pass a pointed piece of wood down his throat, and out at one of his legs. This torture makes the poor frog perspire very much, especially on the back, which becomes covered with white froth: this is the most powerful poison that he yields, and in this they dip or roll the points of their arrows, which will preserve their destructive power for a year. Afterwards, below this white substance, appears a yellow oil, which is carefully scraped off, and retains its deadly influence for four or six months, according to the goodness (as they say) of the frog. By this means, from one frog sufficient poison is obtained for about fifty arrows."

Cochrane's *Travels in Colombia* seems not to have been widely read. A few later observers independently verified this curious use of frogs, however, and unsuccessful attempts were made to analyze samples of the poison scraped from Indian darts. The Swedish anthropologist S. Henry Wassén carried out field investigations in Colombia in 1934 and in 1955. Wassén determined that frog poison was used by two related Chocó Indian groups along the San Juan River. The frogs he obtained from the Indians, erroneously identified by zoologists as *Dendrobates tinctorius*, were actually *Phyllobates aurotaenia* and *P. bicolor*. Wassén also got some frog-poison darts from an isolated group of Chocó far to the south, on the Saija River. The frogs at this locality were collected by our colleague Borys Malkin and us in the early 1970's. Our specimens represented an undescribed species, which proved to contain at least 20 times more poison than its relatives along the San Juan. Because of the frog's awesome toxicity, we gave it a name with obvious connotations: *Phyllobates terribilis*.

The northern Chocó Indians poison their darts with the secretions of *P. bicolor* and *P. aurotaenia* much as described by Cochrane a century and a half ago. The frogs are impaled on a stick and are sometimes held near a fire before the darts are poisoned. The southern Chocó Indians, however, poison their darts simply by wiping them across the



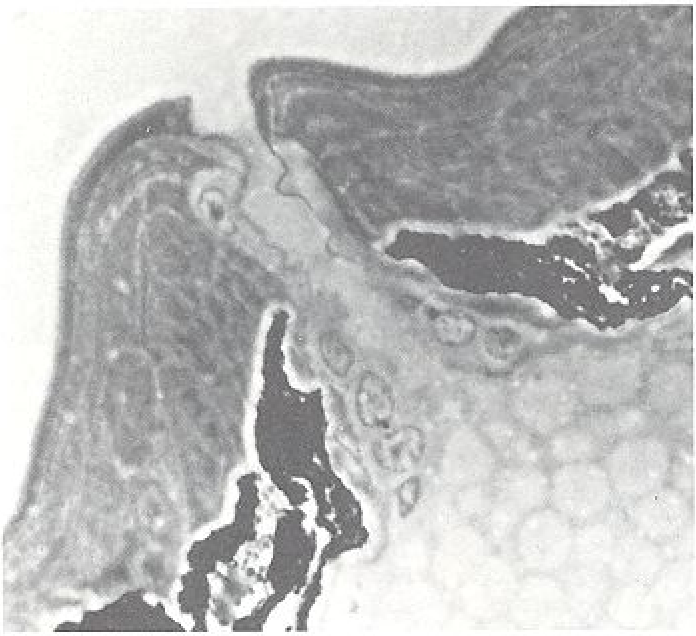


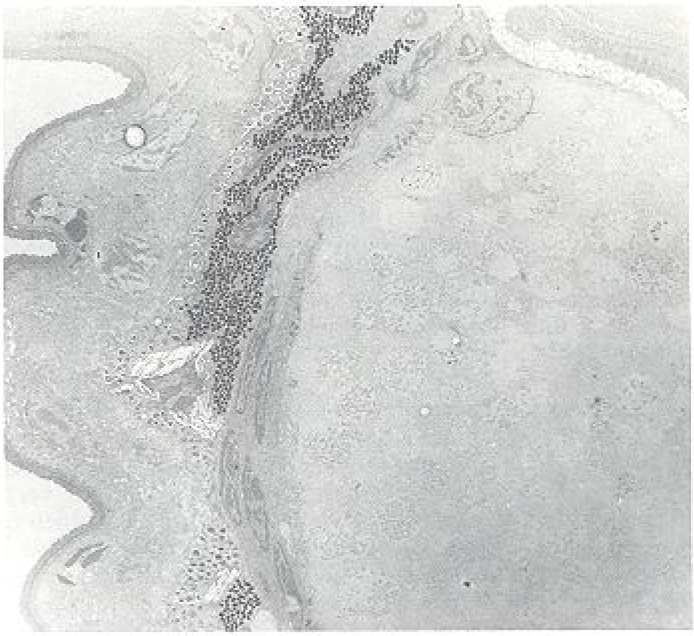
"NURSE" FROGS carry their tadpoles to a suitable body of water after hatching. A female of the species *Colostethus inguinalis* from Panama (*left*) is shown with a load of 27 tadpoles. A male of the small Peruvian species *Dendrobates reticulatus* (*right*) carries only one. The young may remain attached to the parent in this manner for a few hours or for more than a week.

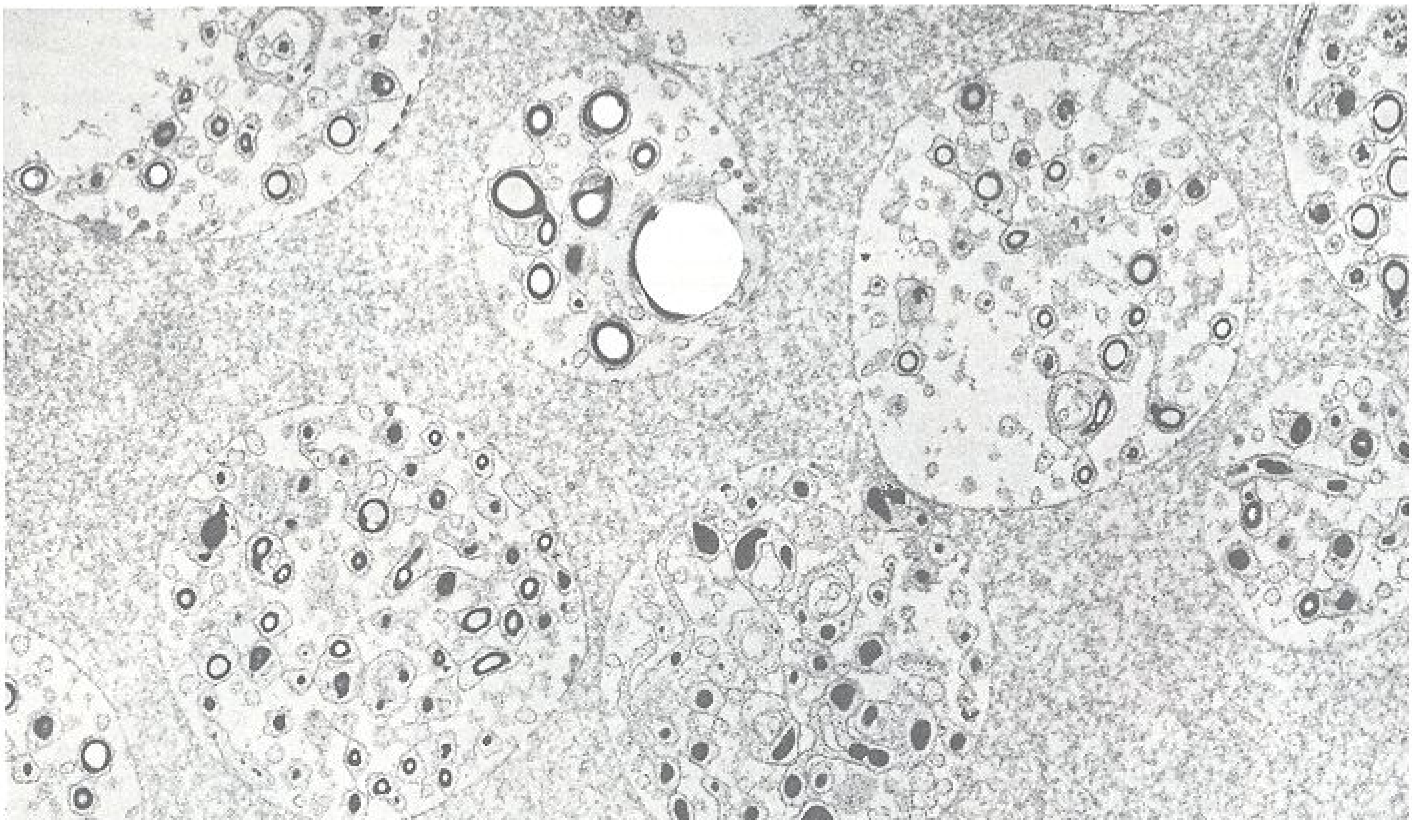
back of a living specimen of *P. terribilis.*

Today reliance on the blowgun is declining among the Chocó, mainly because of increased accessibility of firearms. Contrary to some literary accounts, dendrobatid frogs are not used for poisoning arrows, and their use for poisoning blowgun darts does not seem to have been widespread. This is understandable in view of the fact that the three most toxic dendrobatids are limited to relatively small areas of western Colombia. Two other species of *Phyllobates* are found in Central America, but they have much less toxin than their Colombian relatives and their range is outside the area where dart poisons are known to have been employed.

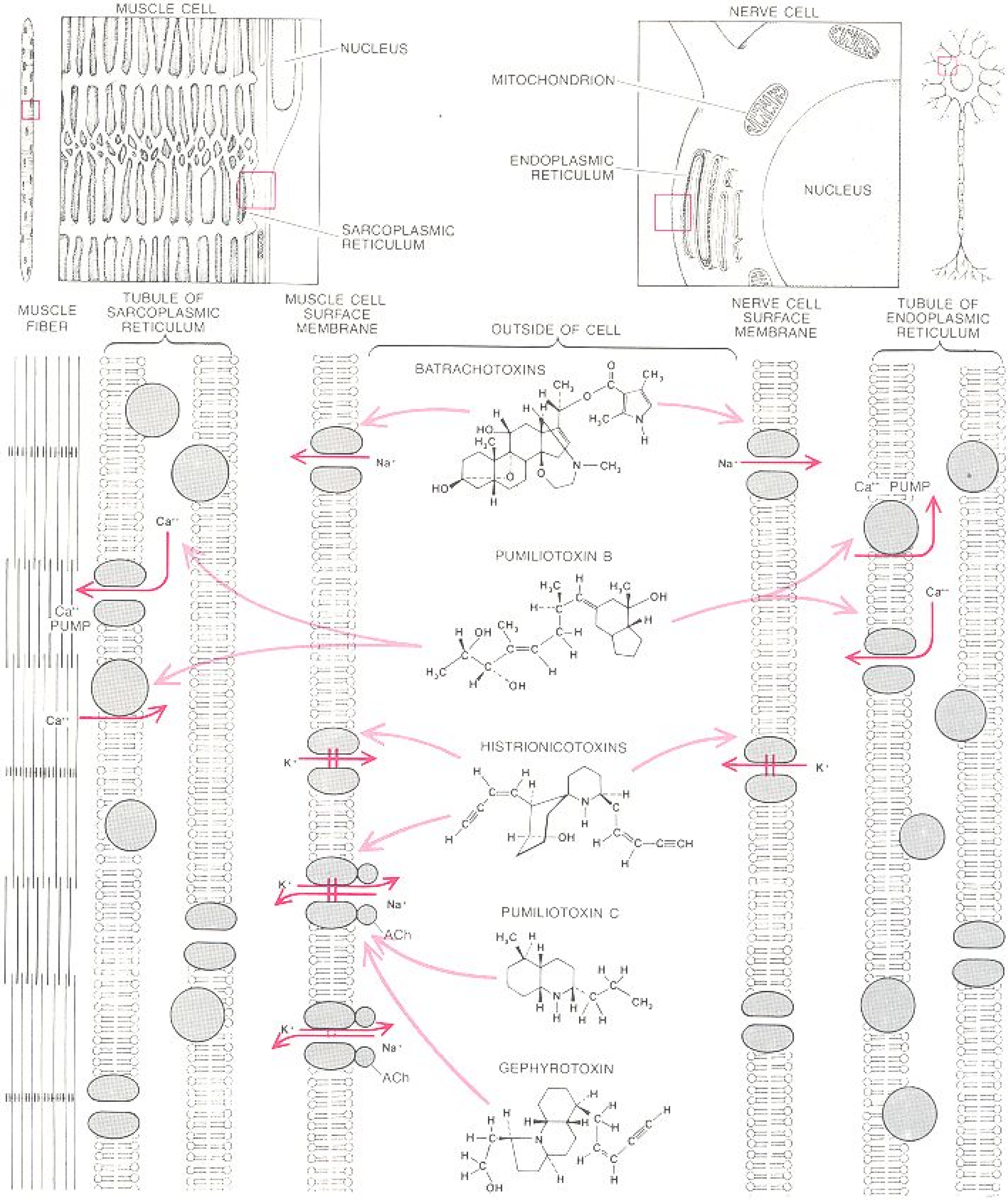
The skin organs that secrete the dendrobatid toxins are "granular" glands whose minute openings are scattered over the surface of the skin among the openings of the frog's mucous glands. Granular glands seem to be a primitive







"GRANULAR" GLANDS OF THE SKIN store and probably manufacture the toxic secretions of dendrobatid frogs. The photomicrograph at the top left shows a vertical section through the upper part of such a gland, magnified 900 times. The gland is filled with large, circular granules; the duct of the gland penetrates a layer of pigment cells and passes through the epidermis to open onto the surface of the skin. The electron micrograph at the top right shows a section through a gland, magnified 1,500 times. Vesicles in the granules may contain enzymes involved in the synthesis of the toxins. The electron micrograph at the bottom shows granules and the vesicles within them magnified 13,000 times. The micrograph at the top left shows a gland of *Dendrobates tricolor*, the other micrographs a gland of *D. auratus*.



MOLECULAR SITES OF ACTION for four kinds of alkaloid compounds from dendrobatid frogs are displayed schematically for muscle at the lower left and for nerve at the lower right. The morphological features of a muscle cell are shown at the upper left, those of a nerve cell at the upper right. In the middle are the structural formulas for the alkaloids. Batrachotoxin prevents the closing of sodium-ion channels in the surface membrane of both muscle and nerve cells. The influx of sodium ions electrically depolarizes the membrane and halts muscle and nerve function. Pumiliotoxin *B* appears to act in two ways. First, it facilitates the release of calcium ions from storage sites inside the muscle cell, thereby potentiating muscle contraction. Second, it inhibits the return of calcium ions to the storage sites, thereby prolonging the contraction. Pumiliotoxin *B* also affects the translocation of calcium in nerve cells. Histrionicotoxin blocks both the outward movement of potassium ions through potassium-ion channels of the surface membrane of muscle and nerve cells and the two-way exchange of sodium and potassium ions through complexes of ion channels and acetylcholine (ACh) receptors in the "end plate" between a nerve fiber and a muscle cell. The blockage of potassium-ion channels promotes the contraction of the muscle cells and prolongs the release of neurotransmitters by the nerve cells. The blockage of the ion-channel/acetylcholine-receptor complexes prevents the acetylcholine released from nerves from triggering muscle contraction. Both pumiliotoxin *C* and gephyrotoxin also block the movement of ions through the ion-channel/acetylcholine-receptor complexes, preventing acetylcholine from triggering muscle contraction.

characteristic common to all frogs. They were evidently a convenient evolutionary preadaptation in some groups of frogs for the synthesis, storage and release of various biologically active secretions.

The active principles of the dendrobatid skin secretions are alkaloids: nitrogenous ring compounds. Although such compounds are found more often in plants than they are in animals, dendrobatid frogs have proved to be a rich source of unique alkaloids. We have collected dendrobatids throughout their range in the tropical Americas for later analysis of their defensive secretions. This work has resulted in the discovery of a dozen new species of poison frogs and more than 200 new alkaloids, the latter representing at least five distinct classes of compounds. Chemical investigation of the frog alkaloids was initiated at the National Institute of Arthritis, Metabolism, and Digestive Diseases by Bernhard Witkop in the early 1960's. Over the past two decades major contributions to this research have been made by Isabella L. Karle, an X-ray crystallographer at the Naval Research Laboratory, and by Takashi Tokuyama, a chemist at Osaka University. The basis for the activity of each class of dendrobatid alkaloids is of considerable interest. The pharmacological investigation of these compounds has been pioneered by Edson X. Albuquerque of the University of Maryland School of Medicine.

The large majority of dendrobatid alkaloids include within their molecular structure a ring consisting of one nitrogen atom and five carbon atoms: a piperidine ring. Simple piperidine compounds are found among all subgroups of the genera *Dendrobates* and *Phyllobates*. From an evolutionary perspective this is evidence that the frogs in these genera form a separate lineage within the family Dendrobatidae. In the five species of the genus *Phyllobates*, however, the biosynthesis of piperidine alkaloids has been largely suppressed in favor of the synthesis of a new class of extraordinarily toxic alkaloids. They are the batrachotoxins (from the Greek *batrachos*, frog), which are the main basis of the poison on the Chocó blowgun darts. These complex alkaloids are structurally related to steroids but have many features hitherto unknown among natural compounds.

The batrachotoxins are among the most potent naturally occurring nonprotein toxins. They selectively increase the permeability of the outer membrane of nerve and muscle cells to sodium ions. This effect results in an irreversible electrical depolarization of the cells, causing in the heart arrhythmias, fibrillation and failure. The specific site at which batrachotoxin acts is associated with the channels that regulate the flow of sodium ions through the cell membrane. Such sodium channels play a key part in the conduction of electrical impulses by nerve and muscle cells. The binding of batrachotoxin prevents the normal closing of the channels. As a result there is a massive influx of sodium ions and the cell is depolarized. Nerve cells can no longer transmit impulses and muscle cells remain in an activated, contracted state. The use of batrachotoxin in research has yielded important new knowledge of the function of sodium channels.

The other dendrobatid alkaloids are all much simpler in structure than batrachotoxin and are much less toxic, but they are no less interesting. Many of these piperidine alkaloids act on an ion channel in the "end plate" at the junction between a nerve fiber and a muscle cell. This channel is associated with a receptor for the neurotransmitter substance acetylcholine. The interaction of the neurotransmitter and its receptor opens the channel in the cell membrane through which both sodium and potassium ions can flow. If the resulting electrical impulse is large enough, it can trigger the opening of separate sodium channels in the membrane. With muscle cells this process causes the release of calcium ions inside the cell, which leads to contraction.

Histrionicotoxins, unusual spiropiperidine alkaloids first isolated from the frog *Dendrobates histrionicus*, interact with sites on the complex formed by the end-plate channel and the acetylcholine receptor, thereby blocking the passage of ions. Such blockage can prevent the transmission of signals from nerve to muscle, an end result similar to the one brought about by curare. Histrionicotoxins also block the passage of ions through separate potassium channels. When these channels are open, potassium ions flow out of both nerve and muscle cells, allowing them to return to their "resting" state after nerve transmission or muscle contraction. The blockage of such channels can lengthen the transmission of nerve messages and prolong muscle contraction.

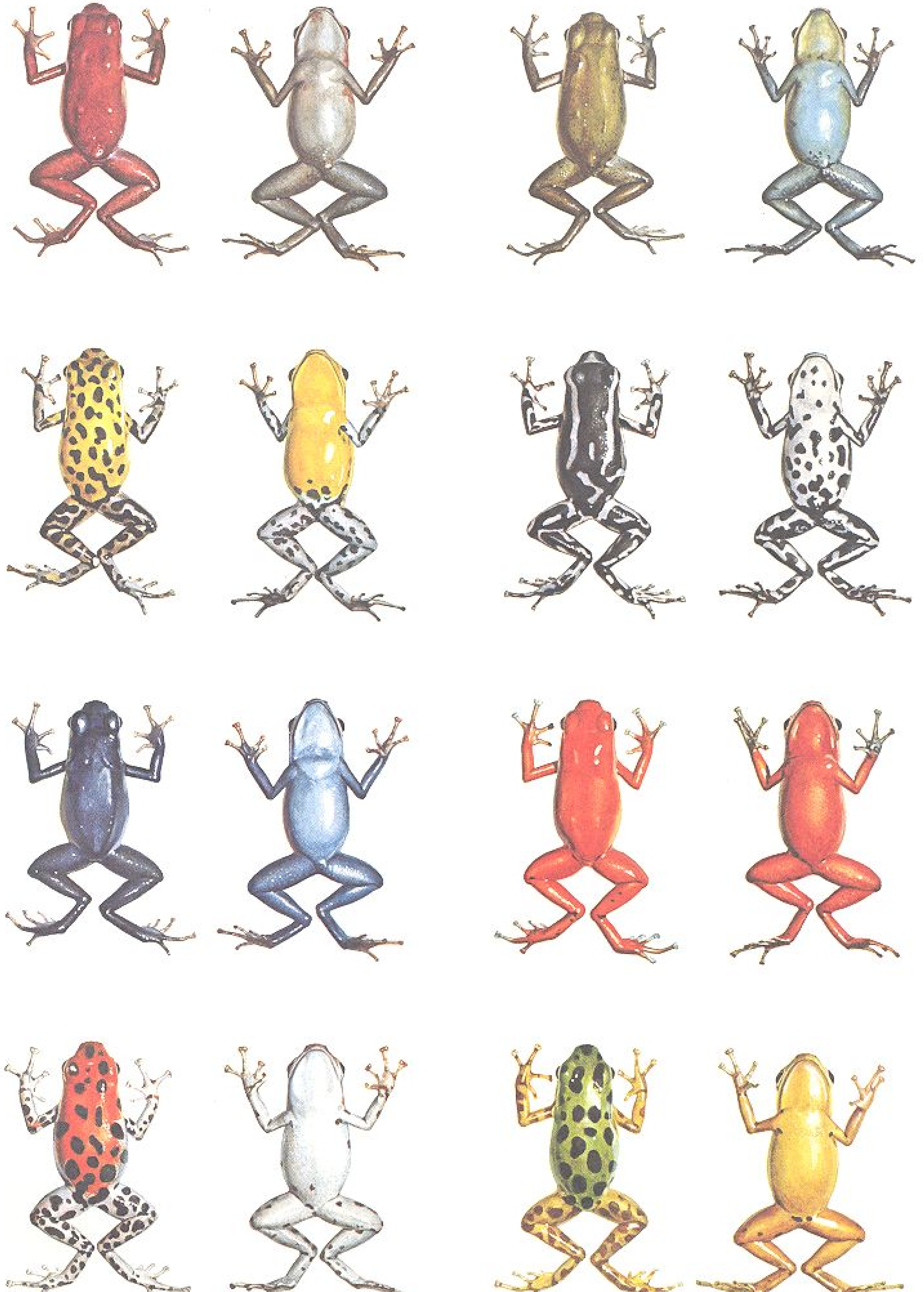
Pumiliotoxin *B*, a unique indolizidine alkaloid first isolated from the frog *D. pumilio*, appears to affect the transport of calcium ions. In muscle cells an electrical impulse causes the release of calcium ions from internal storage sites. The ions then interact with intracellular proteins of muscle and cause contraction. Rather than blocking this process, pumiliotoxin *B* seems to facilitate it and also seems to delay the return of the calcium ions to their storage sites. As a result the force of contraction is augmented and contraction in both heart and skeletal muscle is prolonged. Such tonic actions on muscle may lead to clinical applications for this class of alkaloids.

Dendrobatid frogs with toxic or noxious secretions are usually brightly colored. As is often the case with noxious animals, these species are mimicked by a few other species of frogs. An example is *Eleutherodactylus gaigeae*, which is found together with *Phyllobates lugubris* and *P. aurotaenia* and in the intervening territory, where an ancestral form of *Phyllobates* probably once lived. Unlike the dendrobatids it resembles, the nontoxic *E. gaigeae* is active at night. By day, however, it is sometimes found in the leaf litter where the *Phyllobates* species seek shelter when they are pursued. The different activity cycles may therefore be inconsequential as far as potential daytime predators are concerned.

The genus *Phyllobates* shows less variation than the genus *Dendrobates*, the species of which exhibit a remarkable variety of colors and patterns. Many *Dendrobates* species have primitive striped patterns, but others have evolved colorations that are uniformly bright or variously spotted, banded or mottled. Such variation may even occur among populations of the same species. It would be of much interest to know how such variability originates and whether it bears on the origin of new species. One species in particular, the Central American *D. pumilio*, seems most likely to yield answers to these basic questions.

D. pumilio is a small frog, usually found at elevations below 500 meters in the rain forest on the Caribbean side of Nicaragua, Costa Rica and western Panama. Variability is relatively low in Nicaragua and Costa Rica, where the frogs are usually red or reddish orange with black or bright blue hind legs. In Panama, however, variability is extremely high. It is associated with the geologic history of western Panama. Starting about 12,000 years ago the rising level of the sea created an archipelago of offshore islands and on the adjacent mainland a mixture of lowland swamp forest and rain forest. The archipelago had probably been created and reconnected to the mainland several times before. The populations of *D. pumilio* in the region show all the colors of the spectrum from red to blue; one population is even patterned solely in black and white. The different populations look like differ-

EIGHT FROGS representing different populations of *Dendrobates pumilio* are shown in dorsal and ventral position in the painting on the opposite page. These samples show only part of the extraordinary divergence among frogs of the *D. pumilio* population complex on the Caribbean side of western Panama. All the frogs are shown at the same size, but in life they vary in size as well as in color; they are also remarkably diversified in behavior and in the alkaloids of their defensive secretions.



ent species, and in fact we believe the complex includes at least two species. Nevertheless, most of the variation is found in what seems to be the single species *D. pumilio.*

The variation is not due simply to the independent evolution of populations isolated on islands; different parts of a single island may be inhabited by very different populations. There are also instances of intense variation within single populations. One example we have studied over a period of years is found at the northwestern end of Bastimentos Island. There the color of the frogs' backs varies from orange red through bronze to metallic green. In one beachfront forest orange red frogs consistently made up about 96 percent of the population samples we took each year, with only about 4 percent of the samples showing other colors. In a forest-shaded cacao grove away from the beach, however, the orange red frogs accounted for 84 percent or less of the samples, with bronze and green frogs now constituting as much as 32 percent of the yearly totals. These consistent differences between populations of a species in different habitats are an example of "balanced polymorphism." The phenomenon is probably the genetic basis for some of the striking differences among populations of *D. pumilio.*

Although very different populations of *D. pumilio* are usually separated by stretches of forest not inhabited by the frogs, we found areas on the mainland of Panama where nearly pure populations of red frogs were in contact with similarly pure populations of green ones. Frogs of the other color were rare in both populations. A few other rare color variants in the two populations resembled frogs of more distant populations. These findings further indicate that frog populations of different colors can arise from a common gene pool.

There is more to the *D. pumilio* problem than color. The frogs in the different populations also vary in size and behavior. Their usual habitat can be on the ground or in the trees; their response to potential predators ranges from secretive and wary to bold and apparently fearless. None of these traits seems to be correlated with the frogs' defensive skin secretions, the variations in which are equally remarkable. The *D. pumilio* populations of western Panama overall produce more than 80 alkaloids representing all major classes of piperidine toxins. The number of different alkaloids secreted by frogs of individual populations ranges from six to 24, and many of these compounds have not been detected in other dendrobatid frogs. *D. pumilio* is clearly a leading candidate among all vertebrate animals for the title "most variable species," but we are a long way from understanding all the factors that have made it so.

The Authors

CHARLES W. MYERS and JOHN W. DALY have worked together since 1966, "dividing our time between jungle camps and modern laboratories in a multidisciplinary approach to the biology and biochemistry of poisonous frogs." Myers is chairman of the department of herpetology at the American Museum of Natural History. He received a B.S. at the University of Florida in 1960 and an M.A. at Southern Illinois University in 1962. He interrupted his doctoral studies to spend three years (1964–67) as a visiting scientist at the Gorgas Memorial Laboratory in Panama. He joined the staff of the American Museum in 1968 and got his Ph.D. from the University of Kansas in 1970. Daly is chief of the laboratory of bioorganic chemistry at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. He obtained a B.S. in 1954 and an M.A. in 1955 at Oregon State College and a Ph.D. in chemistry from Stanford University in 1958.

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