Progress in clinical dermatology is derived from new diagnostic and therapeutic approaches and requires increased understanding of the cellular and macromolecular basis of physiology and pathophysiology. Researchers are excited and animated by their experiments and data, yet the research literature frequently fails to convey this immediacy. Why? In part, the convention and form of scientific journals and the eschewing of speculation make the literature inaccessible to the nonscientist. This section of the ARCHIVES will select broadly from the research literature relevant to dermatology and will attempt to integrate what is new in the research laboratory with the physicians' knowledge. Readers' comments are solicited.

Skin Potions

Skin and its appendages have, through the ages, arguably been the source of more potions, both therapeutic and toxic, than any other animal organ. Powders of rhinoceros horn, which consists of no more than compacted stratum corneum, to this day are valued for their aphrodisiac properties. Bezoars, concretions of hair found in stomachs of mountain goats, were worn as amulets to ward off evil spirits or were powdered and ingested as all-purpose antitoxins. Even before the current wave of escalating claims that various skin extracts preserve or restore cutaneous health and beauty, lanolin, the sebaceous secretion that accumulates on sheep wool, was widely accepted for its ability to put "life" back into dreary skin.

The science of skin extraction was probably engendered by frog's skin, long used in the Orient to treat dropsy and by South American Indians to poison arrowheads.[1] Frog's skin has two glandular structures which are located in the dermis and open directly to the surface through short ducts. The "clear" or mucous glands are widely distributed throughout the skin and consist of a simple cuboidal epithelium that continually secretes a clear, viscous material. The "granular" or "poison" glands are concentrated around the neck and central back and produce a milky, holocrine discharge following intense adrenergic stimulation. Regeneration of these glands takes several weeks following discharge, during which time distinctive granules accumulate first in a cellular syncytium and then in a large, acellular, membrane-bound sac.[2] Many of the frog's "toxins" have been localized to these epithelial, granular glands; others appear to derive from nerve endings; the remainder have been localized only to skin.

The use of skin as the source of interesting molecules rather than magic began nearly a century ago with attempts to chemically identify the toxic activities in frogs' skins. There are over 2000 species of frogs, and each species has its own mixture of cutaneous "toxins." Hundreds of biologically active molecules have been isolated from frogs' skins, and most can be classified chemically as biogenic amines, alkaloids, or peptides. Many of these molecules were first isolated from frogs; thus, they have been named for the genus or species in which they were discovered.

Epinephrine and serotonin are representative of the biogenic amines that are widely distributed in frog's cutaneous venom; bufotenine, originally isolated from *Bufo* species, is a dimethyl derivative of serotonin. Bufogenines, also from *Bufo* species, are steroid alkaloids with inotropic actions similar to digitalis and are probably responsible for the therapeutic action of secretions from certain frogs.[1] Batrachotoxins, steroid alkaloids from *Phyllobates* and *Dendrobates* species, are among the most potent toxins known. They are found in the cutaneous secretions used as dart poisons and can cause death within seconds by irreversibly increasing cell membrane permeability to sodium.[3] Chemical identification of these toxins and subsequent chemical modification in the laboratory have been the life work of many individuals and of substantial interest to the pharmaceutical industry.

The most recently discovered, and, in some ways the most intriguing, "toxins" from frog's skin are peptides.[4] During the past 25 years, it has been shown repeatedly that peptides from frog's skin are structurally and functionally similar or identical to mammalian neuropeptides or gut hormones. In many cases, these peptides from frogs were sequenced and their pharmacologic activities characterized before homologous mammalian peptides were known. Some of these peptides, such as bombesin, were first isolated from frog's skin and subsequently found in mammalian tissues. Others, such as physalaemin, were found to be structurally related to known

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mammalian peptides only after they were sequenced.

Bombesin is a tetradecapeptide isolated from *Bombina* species. It is the prototype for a new class of pharmacologically active peptides, whose most interesting actions are to stimulate the release of other hormones (thus, the related mammalian peptide is called gastrin-releasing hormone) and to act as autocrine growth factors.[5] Caerulein, originally isolated from *Litoria caerulea*, shares considerable sequence homology with cholecystokinin and is more than ten times as potent in causing gallbladder contraction—an observation that has already found clinical application. The skin of one *L caerulea* contains enough caerulein to use in 3000 cholecystograms or to treat 50 000 attacks of biliary colic in man.[6] Physalaemin, from *Physalaemus* species, is representative of a group of frogs' peptides that are structurally and functionally related to substance P from mammals.

Why does frog's skin make so many potent molecules? Protection and propagation are the likely explanations. Predatory animals have been observed to regurgitate frogs that have been swallowed whole and some frogs can be housed in the same vivarium with normally voracious turtles and crocodiles. Presumably, the bitter taste of the cutaneous discharge rapidly spoils the appetite of the attacker. Nonetheless, these chemical weapons, which in nature are used exclusively for defensive purposes, are extraordinarily toxic. Fifty micrograms of dried secretion from a single frog contain sufficient toxins to kill 1000 mice when administered subcutaneously.[3]

The moist skin of frogs might be expected to provide a favorable environment for microbes and parasites. Moreover, at temperatures below 15°C, frogs are immunologically paralyzed; they can neither mount antibody responses to foreign antigens nor reject homografts.[7] Bufotenine and some of the alkaloids in frog's skin have significant antimicrobial activity and may serve as the frog's first line of defense.[8]

Several species of desert frogs may share the same pond. During the copulatory frenzy that follows the first rains of the year, mismatches are not uncommon. A struggling female that cannot gracefully escape the clutches of an incompatible male will release a poison from her cutaneous glands that weakens or even kills him, thereby increasing the chance that her eggs will not be wasted.[9]

An important unanswered question about these biologically potent skin products is whether they have a role in regulating the internal environment, as well as the external environment. It is clear that a complex and varied array of chemical signals and mediators evolved in the skin of amphibians as they emerged from the ancient sea. Current investigations are discovering biologically active molecules in human epidermis that may serve as autocrine or paracrine growth regulators or as immunomodulators. We should not be surprised if modern attempts to extract human skin reveal a wealth of potent molecules whose functions range from the vital to the vestigial.

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