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Adaptive evolution of secretory cell lines in vertebrate skin

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Abstract — The embryonic horny layer of vertebrates contains distinctive cell lines that account for the remarkable, diverse secretory performances of their cutaneous apparatuses. Aquatic classes (jawless, cartilaginous and bony fishes) possess single gland cells, scattered among ordinary epidermal cells, that manufacture proteinaceous or mucous substances. This dichotomy is retained in adult amphibians, although the secretory cells in anamnionic tetrapods begin to be arranged in complex glands located in the loose dermis. In the Amniota, intensive keratinisation involving the epidermis results in the loss of the ancestral secretory lines, accompanied by the onset of a novel, lipid-producing gland type, which in mammals is flanked by the exclusive sweat gland apparatus.
In this concise up-to-date review, we attempt to phylogenetically narrow the large variety of secretory structures in vertebrate skin into a few basic schemes, in the light of the close relationships between environmental challenges and ecological, ethological as well as physiological roles of the cutaneous apparatus.

Key words: Cutaneous glands, function, structure, ultrastructure, vertebrate phylogenesis

INTRODUCTION

Along with ordinary cells, which produce keratins and perform mechanical roles, the epidermis of anamnionic vertebrates includes various cell populations involved in secretory processes. Despite their wide morpho-functional variety, these secretory cells fall within a main dichotomy, splitting into mucous and proteinaceous cell lines (Quay 1972). These mucus and protein secreting cells follow similar fates during vertebrate phylogenesis: in primary aquatic classes (cyclostomes, cartilaginous fishes and bony fishes), the skin cell glands are single, whilst in amphibians the cells are arranged in multi-cellular glands deriving from intraepidermal buds and reaching their ultimate position in the loose dermis during ontogenesis. As a border line class, during the larval phase, amphibians have single intraepidermal cells with a putative gland role, but as adults their dermis is packed with multicellular glands, whose biosynthetically active part (secretory unit) is connected to accessory structures with specific roles (Delfino 1991).

The transition from the aquatic to the subaerial environs is adaptively correlated to an increase in keratin production in the ordinary epidermal cells (keratinocytes), along a basal – surface layer gradient. Intra-cytoplasmic keratin accumulation is a peculiar apoptotic process which leads to the formation of an external horny layer. The development of this coat of dead cells provides the organism with an efficient protection against dehydration, but in reptiles, birds and mammalians it is consistent with loss of both mucous and proteinaceous glands. However, the massive keratinisation in these classes is accompanied by the appearance of a novel gland type, producing lipids (sebum), which in mammals culminates in the formation of the pilo-sebaceous organs. These are complex functional units, which include hairs and lipid-producing glands. Furthermore, mammalian evolution is marked by the development of cutaneous glands that, despite the differences in the shape and function of their secretory units, share certain structural traits with the multicellular glands of amphibians: the tubular, sweat glands.

This synthetic survey outlines the continuity of epidermal secretory cell lines throughout vertebrate phylogenesis as a result of their adaptive plasticity. In the light of such functional flexibility, our review will analyse vertebrate cutaneous glands within an evolutionary context, with the

aim of pruning their large morphological and physiological variety to fit just a few basic structural types, moulded in response to external environmental challenges. With this scope in mind, we shall only consider strictly cutaneous glands, overlooking both secretory organs at the mucous-cutaneous junctions (which include glands of possible entodermal origin), and salivary glands (stomodeal in origin), although the latter are regarded as derivatives of the outer embryonic germ layer (ectoderm). As mammary gland bodies play a pivotal role in mammalian brood rearing, rather than in cutaneous physiology; they have also been disregarded in this review, albeit their secretory units are homologous to apocrine sweat glands.

Although adequate attention will be paid to the phylogenetic relationships between the taxa considered, most concepts raised in this paper deal with cyto-histological and physiological aspects that provide ample representation of the secretory performances of the vertebrate epidermis. Our review includes an essential set of unpublished micrographs collected from routine light (LM) and transmission electron microscopes (TEM).

Unicellular Glands

The most representative secretory cells in ichthyopsidan skin are the mucocytes specialized as goblet cells, widespread in jawless, cartilaginous (Fig. 1A) and bony fishes (Figs 1B and 1C), but absent in extant Agnatha of the genus *Petromizon*. Goblet cells are responsible for the production of the slimy layer that covers the body surface of these aquatic vertebrates, with further contribution from the ordinary, outer epidermal cells. The surface mucus plays several roles relevant to fish survival in the aquatic environ: it reduces body-water friction; contributes to hydro-saline homeostasis (ABRAHAM *et al*. 2001); mediates gas (ZACCONE 1981) and heat exchanges, and also keeps infective agents away from the epidermal layers. In extant lung fishes of the genera *Protopterus* (Fig. 1B) and *Lepidosyren*, epidermal mucocytes pro-

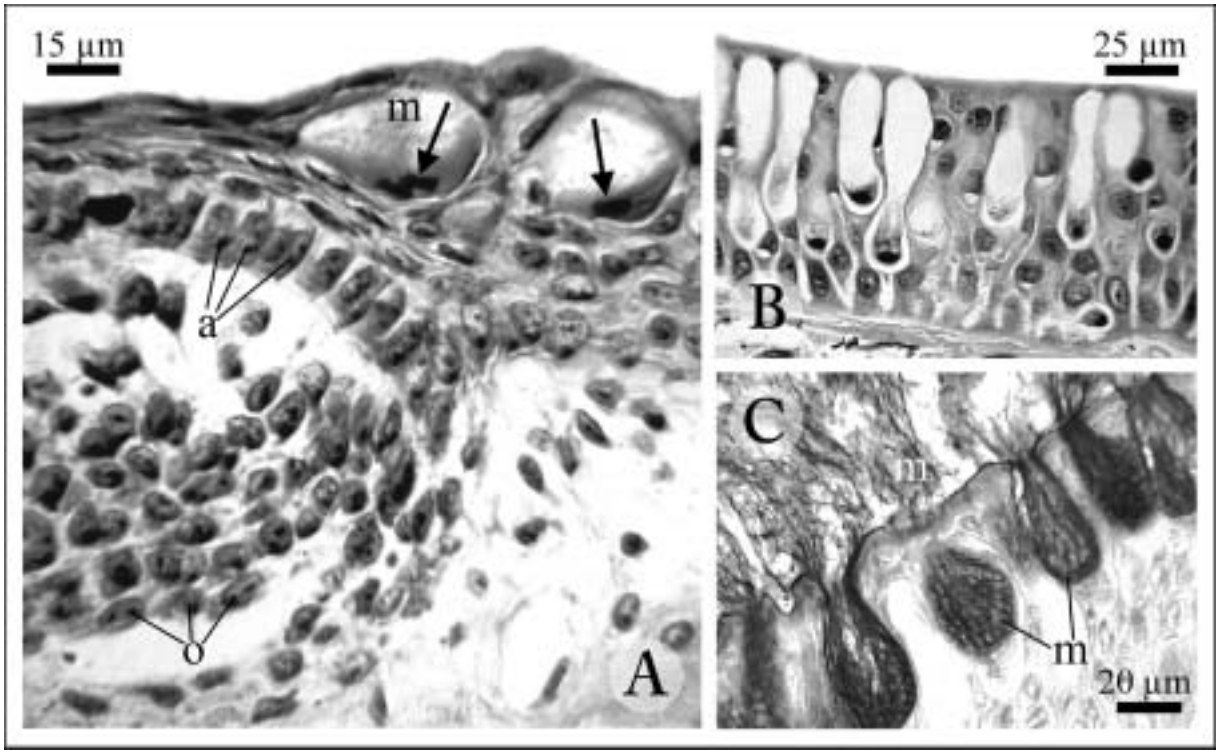

Fig. 1 — Unicellular epidermal glands in cartilaginous and bony fishes under the light microscope. A: In this shark (undetermined species) mucous producing cells are ellipsoidal in shape, although they display somewhat polarisation with basal nuclei (arrows) and apical cytoplasm containing secretory product (m); notice the placoid scale Anlage in the dermis with enamel cells (adamantoblasts, a) and odontoblasts (o); hematoxylin-orange. B: In this lungfish (*Protopterus* sp.) the epidermis contains numerous goblet cells which produce the mucous contributing to the formation of the cocoon during aestivation; hematoxylin-eosin. C: In the lip skin of the eel (*Anguilla anguilla*), semi-specific staining (such as this Mallory's triple stain) reveals the mucous product (m), both intra- and extra-cellular.

duce abundant material that mixes with the mud in the environment and forms a cocoon, protecting these burrowing, air breathing fishes from dehydration during aestivation. Although epidermal mucocytes can vary in shape from spheroid (Fig. 1A) to chaliciform (Figs 1B and 1C), they share a common, functional architecture founded on a basal-apical polarization. The nucleus lies in the lower third of the cell, encircled by a meniscus-shaped cytoplasm, free from secretory material. The upper two thirds are overlain by contiguous epidermal cells which leave an exiguous surface area for secretory discharge (Fox 1989). The upper (apical) cytoplasm contains the product and appears transparent in ordinary LM specimens (Fig. 1B), but the mucous material is evident after partly histochemical staining (Fig. 1C). Selective histochemical trials have revealed that the epidermal goblet cells of bony fishes contain mucopolysaccharides (glycosoaminoglycans) with a low degree of sulphatation (Zaccone 1982a; Sultana and Rao 1990).

The proteinaceous cell type represents a heterogeneous secretory line that includes several categories based on morphological, functional and histochemical traits. Much of the morphological variety of these secretory cells, which seldom open onto the skin surface, is consistent with the extreme specialisations typical of the extant jawless and jawed bony fishes. However, this heterogeneity is also largely due to the subjective criteria that various authors have used for their analyses over the last decades. Although this survey aims to describe proper cutaneous uni- and multicellular glands, we shall also consider peculiar epidermal cells that manufacture complex cytoskeletons, when such macromolecular complexes are functionally associated with cutaneous secretions. The list below follows the criteria of the exhaustive review by Whitear (1986).

Granular (or serous) cells produce and store secretory materials consisting of discrete granules occupying large parts of the cytoplasm. In some instances, these cells exhibit evident polarization with basal nuclei and, despite their spheroidal shape, they have been described as serous "goblet" cells.

Sacciform cells are characterized by high levels of metabolic activity (Zaccone 1982b) and posses a peculiar storage organelle (an inner cistern with a proper limiting membrane) that contains products with various degrees of condensation, ranging from electron-translucent to electron-opaque. These products consist of proteins, lipids and phospholipids (Sultana and Rao 1990), along with tryptophan- and tyrosine-containing or derived molecules (such as 5-HT), involved in regulating synthesis and/or release of skin secretory products, or in chemical defence (Zaccone 1981; 1982a). This defensive role is confirmed by the increase in the number of sacciform cells during infestation by ectoparasitic protists (Pickering and Fletcher 1987). Foreshadowing a biochemical trait common in anuran skin serous glands, sacciform cells synthesizing 5-HT are also programmed to produce neuro-endocrine peptides, so they are also involved in paracrine processes (Zaccone *et al.* 1987; Fasulo *et al.* 1993) relevant to homeostasis of the cutaneous micro-environment.

Club cells are large and sometimes binucleate, they are inserted in the middle layer of the epidermis and do not reach the external body surface. Although definition of this cell type is based on a common shape and a possible secretory role, the consistent trait in club cells is their peculiar peripheral cytoskeleton consisting of single, coiled filaments with various orientations (random to regularly arranged, Whitear 1986) or thick and clockwise ordered bundles of filaments (Downing and Novales 1971). Histo- and cyto-chemical studies detected substances relevant to immune process in these cells (Suzuki and Kaneko 1986; Nakamura *et al.* 2001), along with the biogenic amine 5-HT (Zaccone *et al.* 1990). Club cells in gregarious species of teleostean Gonorhynchiformes and Ostariophysi synthesize alarm substances that, once released, cause fright reaction among members of the group (Pfeiffer 1974, see also giant cells in toad tadpoles). When under saline stress, the skin club cells express phagocytotic activity against leucocytes moving into the epidermis from the dermal compartment (Abraham *et al.* 2001).

Air-breathing bony fishes, both larval lung fishes (Fox 1989) and adult ray-finned fishes (Whitear 1986; Yokoya and Tamura 1992), possess transparent, epidermal cells. As common traits they exhibit "swollen", "vacuolated" or "lucent" inner cytoplasm regions and outer aggregations of tonofilaments. These lucent cells are superficial in larval specimens, but occupy the middle epidermal layer in adults, where the highly hydrated content of their "vacuoles" may regulate water loss according to the terrestrial condition of the fish (Yokoya and Tamura 1992).

Jawless hagfishes possess large intraepidermal thread cells, with single, coiled bundles of intracytoplasmic filaments along with microtubules. These cells contribute to the composition of con-

spicuous secretory organs and will therefore be considered later together with the secretory cell clusters in ichthyopsidans.

Gland-like, epidermal cells (Leydig cells or LC_s) have been described in larval urodeles (FÄHRMANN 1970a; b; FOX 1988; GREVEN 1980), and in the apodan genus *Ichthyophis* (FOX 1986a; b; BRECKENRIDGE *et al.* 1987; FOX 1988). They are spheroidal to ellipsoidal in shape, and their cytoplasm is divided into two distinctive regions (Fig. 2A): a central, "court plasma", containing secretory organelles, and a peripheral region where evident vesicular products are stored. The outer cytoplasm contains a peculiar net (Lagerhans network, LN, FÄHRMANN 1970a; b; GREVEN 1980; ROSENBERG *et al.* 1982; KANTOREK and CLEMEN 1990), which shares some of the features appearing in the cytoskeleton of the club cells in bony fishes, as it consists of 10 nm thick filaments arranged in helicoidal bundles (Fig. 2B). Although in advanced embryos and early larvae LC_s may be engaged in exocytotic processes and discharge their vescicular product into the epidermal interstices (Fig. 2C), their role seems to be prevalently mechanical. LC_s confer structural stability to the epidermal architecture by combining pressure from the fluid content in their vesicles with the constraint exerted by LN.

The epidermis in tadpoles of the clawed toad *Xenopus laevis* contains peculiar cells (*Kugelzellen*, KZ_n, FRÖHLICH *et al.* 1977) that under the LM appear to be roughly spherical (Fig. 2D), but vary in shape under the TEM (Figs 2E and 2F). They have an dense outer cytoplasm and an inner region with translucent background, holding thick tonofilament bundles (Fig. 2E). Although NIEUWKOOP and FABER (1967) have described KZ_n as unicellular glands, they seem to be analogous to notochord cells in their mechanical role as they may sustain the epidermis architecture by acting as *druckelastische Zellkugeln* (FRÖHLICH *et al.* 1977). Indeed, KZ_n form a highly hydrated, intermediate cell layer in the epidermis and resemble urodele LC_s in morphology as well as function (FOX 1988), so that PFLUGFELDER and SCHUBERT (1965) described them as *Leydigsche Drüsenzellen*. KZ_n are also described as clear cells or (intraepidermal) "vacuoles" (SEKI *et al.* 1989) on account of their inner electron-translucent cytoplasm (Fox 1988). However, this trait seems to result from degenerative processes (Fig. 2F) affecting the epidermis in preparation to metamorphosis.

Large (giant) cells (GC_s or *Riesenzellen*) have been described in the larval skin of gregarious bufonids (Fig. 2G). In GC_s the nucleus is basal and the supra-nuclear cytoplasm contains the secretory product (Fig. 2H, and DELFINO 1991) that resembles the granules found in multicellular serous glands of *Bufo* specimens (DELFINO *et al.* 1995a; b). Their prominent smooth endoplasmic reticulum (ser) and typical mitochondria with tubular cristae, suggest GC_s produce steroids (DELFINO *et al.* 1995b). Once released, this cutaneous product acts as an alarm substance, triggering fright reaction in a tadpole school, with a similar reaction to that described in bony fishes (PFEIFFER 1974). It is interesting to note that some steroid derivatives, such as bufotoxin and gama-bufotoxin found in the cutaneous poison of adult bufonids (MEYER and LINDE 1971) also induce fright reaction (KULZER 1954). Most reports suggest that the alarm substance is only released when the skin is injured (KULZER 1954; PFEIFFER 1974), but FOX (1988) described discharge from GC through exocytosis.

Multicellular Glands

Unicellular gland clusters - In the skin of ichthyopsidan vertebrates, secretory cells may form clusters, foreshadowing simple multicellular glands. They usually retain their intaepidermal position and lack specialized ducts.

Among cyclostomes, the hagfishes (Myxiniformes) posses paired and segmental rows of "slime glands" along their flanks, that produce and discharge a gooey material involved in an unusual defense mechanism. The slime gland is saccular in shape and includes mucocytes along with thread epidermal cells. Thread cells possess a polysome machinery which manufactures fibrous proteins, bearing a similarity to some keratin polypeptides in their amino acid compositions (SPITZER *et al.* 1984). In each cell, the fibrous products become aggregated into intermediate filaments (IFs) and thin filaments around an ephemeral microtubule template (TERAKADO *et al.* 1975), to form a single and highly coiled thread. Thread cells are "IF machines" and could elucidate the functional relationships between growing intermediate filaments and associated microtubules (DOWNING *et al.* 1984). *In vitro* experiments demonstrated that the threads interact with substances produced by mucocytes, facilitating mucus hydration, and so modulating its viscosity as well as adhesion to tissue substrates (KOCH *et al.* 1991). When the hagfish is attacked, several liters of hydrated goo are formed in less than a minute,

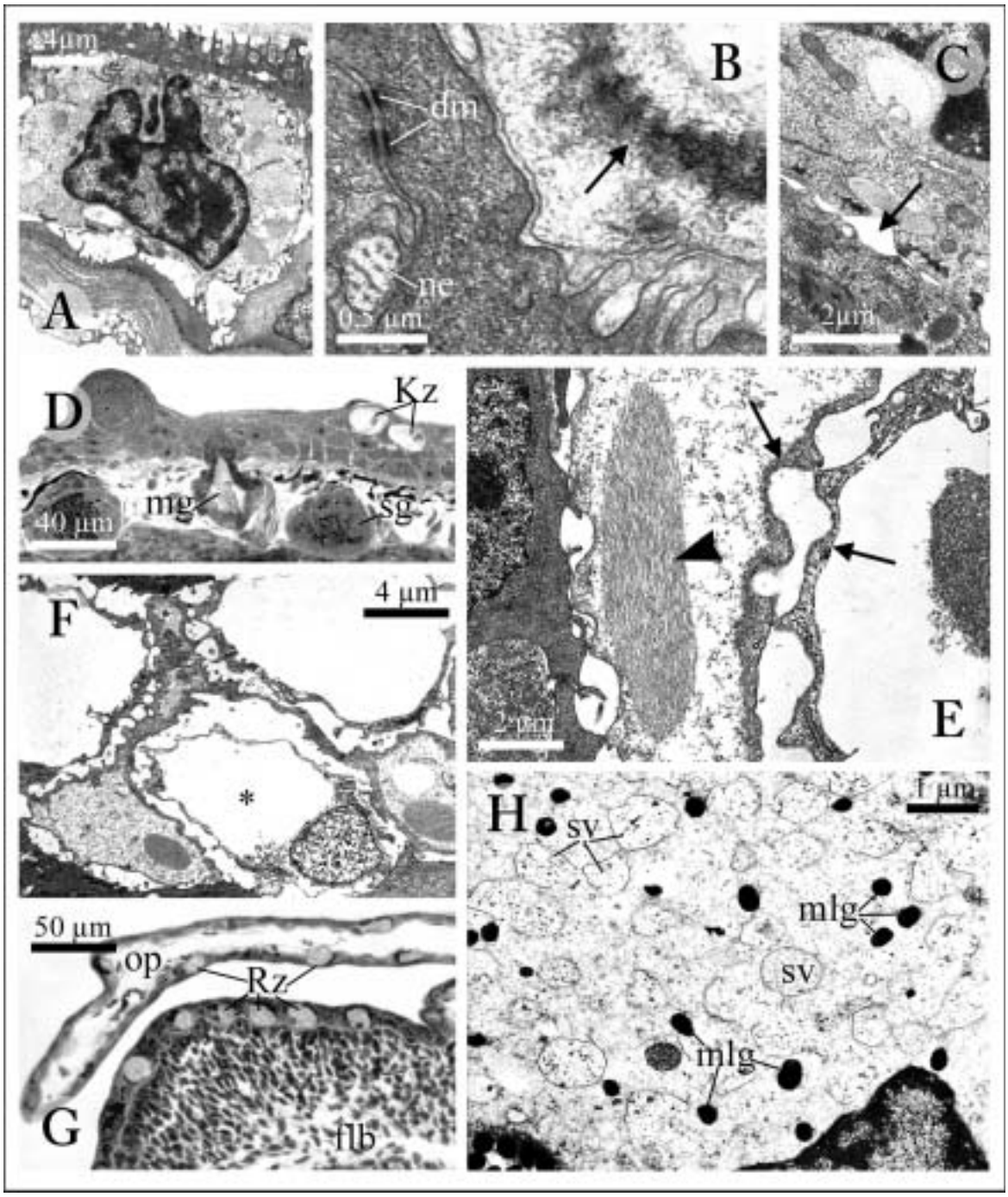

Fig. 2 — Putative unicellular glands in the epidermis of larval amphibians (A,B and C, Leydig cells in the spectacle salamander (*Salamandrina terdigitata*); D, E and F *Kugelzellen* in pre-metamorphic tadpoles of the clawed toad *Xenopus laevis*; G and H giant cells (*Riesenzellen*) in the common Italian toad *Bufo vulgaris*. A, B, C, E, F, H, transmission electron microscope; D, G, light microscope. A: These cells exhibit an obvious central-peripheral polarisation. B: Their peripheral cytoplasm contains coiled tonofilament bundles (arrow); notice desmosomes (dm) and a nerve ending (ne) between keratinocytes C: Early Leydig cell, this vesicle releases its product into the interstice (arrow). D: In this tadpole, intraepidermal *Kugelzellen* (Kz) coexist with intradermal pluricellular glands, mucous (mg) and serous (sg) in nature. E: The same as above, these cells contain conspicuous bundles of filaments (arrowhead) and a dense cytoplasm cortex (arrows). F: However most Kz in this pre-metamorphic stage are involved in degeneration processes (asterisk). G: Toad tadpole before anterior limb eruption, both the epidermis layers in the skin fold covering the gill chamber (operculum, op) and in the forelimb bud (flb) have roundish giant cells (or *Riesenzellen*, Rz). H: The same as above, Rz cytoplasm contains secretory vesicles (sv) and melanin granules (mlg).

covering the gill surface of the predator and even suffocating it.

Ichthyocrinotoxic bony fishes possess groups of secretory cells producing toxins to be delivered in the environment, whereas in acanthotoxic species, the secretory cells are connected to stinging apparatuses (NAIR 1988). In some teleostean species, axillary glands have been described, consisting of assemblages of holocrine cells sharing a common release pore on the skin surface (WHITEAR *et al*. 1991). These secretory cell clusters lie contiguous to the pectoral spine, and therefore foreshadow a chemical defense apparatus, although their function is unknown. Although specialistic evolution led extant cartilaginous as well as bony fishes to develop complex cutaneous secretory structures devoted to chemical skin defense, including spines and modified fin rays (HALSTEAD 1978), the venom producing skin areas resemble assemblages of single gland cells, rather than real organs. Beside toxic and venomous molecules, multicellular glands in fish skin produce substances relevant to hatching and brood care as well as immune defence (WHITEAR 1986).

Multicellular glands of serous and mucous types - In extant amphibian orders (anurans, urodeles and caecilians) multicellular glands are so widespread in the skin that they are considered typical cutaneous annexa in this class of tetrapods. Indeed, the three orders are grouped under the subfamily Lyssamphibia (smooth-skinned amphibians), on account of their scaleless, secretion-moist skin surface. Amphibian cutaneous glands are intradermal organs, mucous, proteinaceous (serous) or mixed in nature (when they combine both secretory lines, DELFINO *et al.* 1986). These organs derive from intraepidermal mother cells, which undergo mitotic processes under the control of thyroid hormones (MCGARRY and VANABLE 1969a; b) and, more distally, of the hypothalamic-pituitary axis (HAYES and GILL 1995). Cell multiplication is accompanied by segregation from the epidermis and down-growth into the dermis (Fig. 3A). Various micro-environmental, inductive influences play specific roles during the gland bud descensus, which are responsible for the cell composition of the mature organ (DELFINO *et al.* 1985). Some cells are only partly involved in down-growth: they remain at the epidermis-dermis interface, maintain an undifferentiated status and form the intercalary tract that represents the stem compartment of the fully developed gland (FARAGGIANA 1938a; 1939; DELFINO 1980). Cells which acquire their ultimate position in the dermis become arranged in two (outer and inner) regions and undergo distinct cytodifferentiation processes. External cells are influenced by direct axon contacts (or at least by neurotransmitters), change into myoblasts and later into smooth muscle cells (DELFINO *et al.* 1987). These myocytes, called myoepithelial cells on account of their contractile role and epidermal origin, exhibit peculiar ultrastructural traits according to the secretory unit type (mucous or serous) they surround (BANI 1976; BANI and DELFINO 1990). The internal cells are adenoblasts pertaining to the epidermal, mucous or proteinaceous secretory lines. The gland duct is actually an intraepidermal interstice, with a straight-course lined by keratinizing cells which allow the external environment to penetrate the epithelial skin layers without causing dehydration.

Intradermal, mucous glands in the skin of extant amphibians share common morpho-functional traits: the secretory unit consists of discrete adenocytes (mucocytes) in varying secretory phases. They are arranged radially and enclose a lumen whose width depends on their height (Fig. 3B). The mucous gland myoepithelium lacks direct nerve supply and performs tonic contractions controlled by neurotransmitters diffusing from free nerve endings, a few hundreds nm apart (WHITEAR 1974; SJÖBERG and FLOCK 1976).

On the contrary, serous glands in anurans differ remarkably from their urodele counterparts in both the secretory and contractile compartments. Serous units in newts and salamanders (LE QUANG TRONG 1967, DELFINO *et al.* 1982b), as well as in caecilians (WELSCH and STORCH 1973) display an epithelial arrangement (Fig. 3C), although the adenocytes are assembled at random and the lumen is exiguous. As stated in pioneering LM studies (FARAGGIANA 1938b), the secretory compartment in anuran serous glands is syncytial in structure with the nuclei forming a peripheral row in the common cytoplasm (Fig. 3D). The secretory syncytium develops in early gland buds during cytodifferentiation, and represents a fundamental, specialized trait in anurans, since it allows coordination of biosynthesis and maturational processes (DELFINO *et al*. 1988) in the common cytoplasm, where the serous product is stored. In both urodele and anuran serous glands, secretory release involves the contractile layer or myoepithelial cells which possess direct innervations (Fig. 4A). Nerve endings are parasympathetic (cholinergic) in newts and salamanders (HOFFMAN and DENT 1977) but orthosympathetic

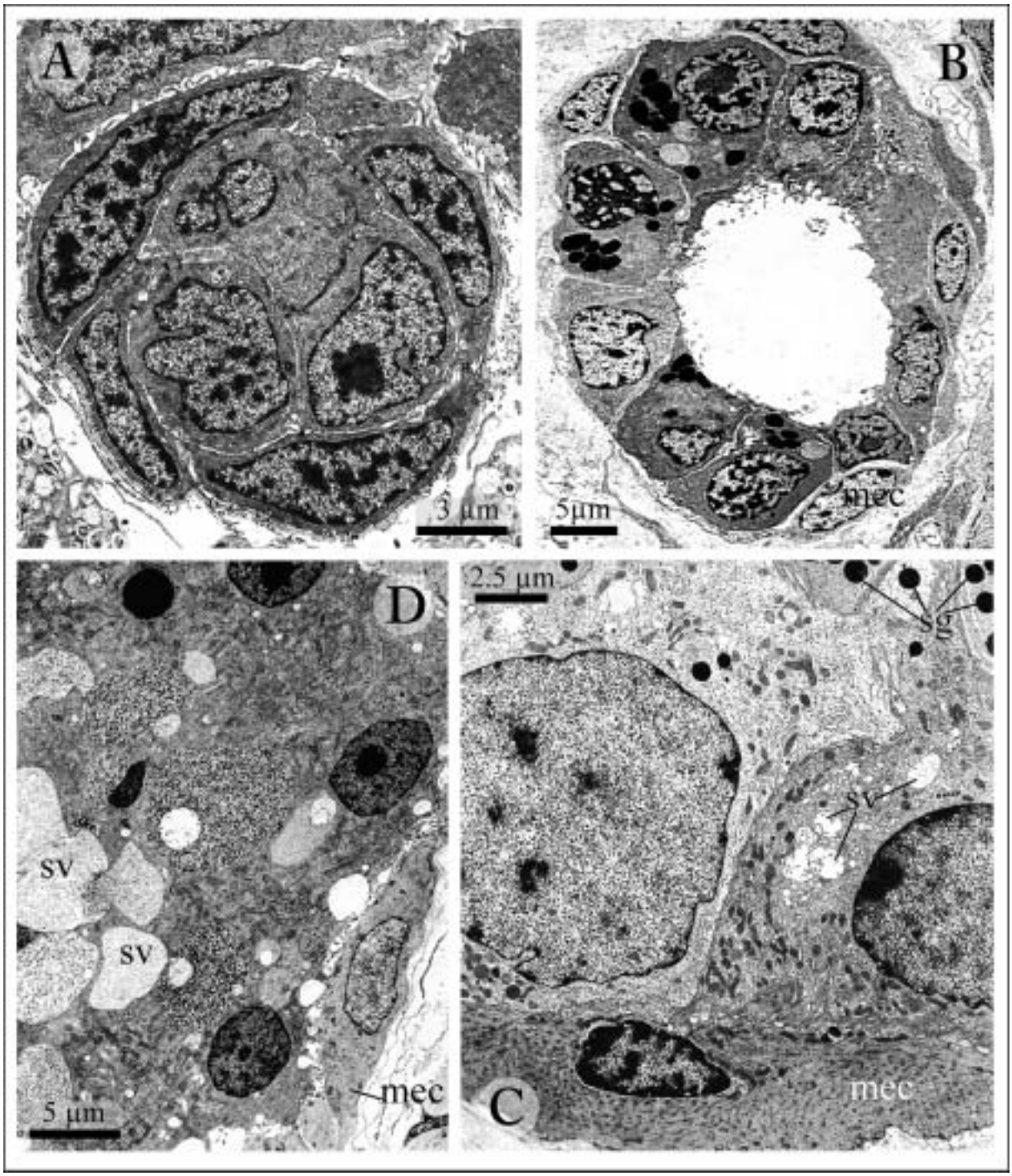

Fig. 3 — Multicellular glands in amphibian skin under the transmission electron microscope (mec = myoepithelial cell). A: Pre-metamorphic tadpole of *X. laevis*, undifferentiated gland bud during down-growth into the dermis. B: Adult *Phyllomedusa hypochondrialis*, the tigerleg monkey tree frog; this mucous gland shows a wide lumen and secretory epithelium in asynchronous activity. C: *S. terdigitata:* urodele serous glands exhibit discrete secretory cells in various functional phases (sg = secretory granules; sv = secretory vesicles). D: Pre-metamorphic tadpole of the Iberian midwife toad (*Alytes cisternasii*): the secretory unit is syncytial in structure and contains secretory vesicles (sv) holding a product involved in maturational condensation.

(adrenergic) in toads and frogs (BENSON and HADLEY 1969; DOCKRAY and HOPKINS 1975; HOFFMAN and DENT 1977; HOLMES *et al.* 1977; HOLMES and BALLS 1978; DELFINO *et al.*1982a; DELFINO *et al.*1990; DELFINO *et al.* 2002; NOSI *et al.* 2002; DELFINO *et al.* 2006). The exiguous lumen of anuran serous glands lies just below the intercalary tract and contains small amounts of secretory material released by constitutive (DELFINO *et al.*1994; DELFINO *et al.*1996; DELFINO *et al.*1999; TERRENI *et al.* 2002) or inducible (SEVINC *et al.* 2005) merocrine processes. Although such a scanty product may be emitted by modulation of mec contractile responses (DELFINO *et al.* 1982a), the muscular sheath usually performs phasic activity and causes "bulk discharge" (DELFINO 1980; DELFINO *et al.*1996; MELIS *et al.* 2000; DELFINO *et al.* 2002; NOSI *et al.* 2002; DELFINO *et al.* 2006) which involves the secretory product and portions of the secretory syncytium as well (Figs 4B and 4C). Such heterogeneous material may pervade the epidermis and reach the interstice beneath the external horny layer (Fig. 4D), passing through the discontinuous duct wall (DELFINO 1976). As discussed later, this functional mechanism contrasts the typical holocriny described in lipid producing glands of amniotic vertebrates.

In extant amphibians, anuran serous glands exhibit a remarkable functional plasticity as they produce a large variety of molecules involved in several adaptive responses. Serous glands are usually poisonous in character, as they produce toxins and repellents, including "modern" alkaloids along with "ancient" regulative molecules (biogenic amines and peptides) primitively involved in skin homeostasis (DALY *et al.* 1987). Some peptides and proteins are responsible for the antimicrobial activity of anuran skin poisons (BACHMAYER *et al.* 1967; CSÓRDAS and MICHL 1969; MICHL 1978; BARBERIO *et al.* 1987; MASTROMEI *et al.* 1991, ZASLOFF 1987; ZASLOFF *et al.* 1988), which are also effective against eukaryotic cells (KISS and MICHL 1962; KAISER and KRAMAR 1967; BACHMAYER *et al.* 1967; MAR and MICHL 1976; MICHL 1978; BALBONI *et al.* 1992; SANNA *et al.* 1993).

Specialized anuran serous glands are inserted among reproductive glands: this is a large and heterogeneous type of exocrine organs, also found in urodeles, that includes mucous units (Brizzi *et al.* 2003). In hylids pertaining to the South American genus *Phyllomedusa*, a serous-derived gland type (DELFINO *et al.* 1998a; b; LACOMBE *et al.* 2000; NOSI *et al.* 2002; SEVINC *et al.* 2005) produces complex storage granules (Fig. 5A) containing a wax-like substance which protects these tree frogs from dehydration (BLAYLOCK *et al.* 1976). In the Australian hylid frog *Litoria caerulea* specialized glands in the head skin as well as ordinary serous units manufacture cutaneous lipids (WARBURG *et al.* 2000). This leads to the assumption that serous glands in xeric-inhabiting, arboreal frogs have evolved a specialized secretory unit exhibiting some functional analogies with the cutaneous lipogenic glands of Amniota.

Sebaceous glands - In reptilian skin, a novel, successful type of multicellular glands appears that shares several morpho-functional traits with mammalian sebaceous and avian preen glands (QUAY 1986a). In this review, they are therefore referred to a common lipogenic class. These glands are exclusive of Amniota, and perform similar functions to the syncytial lipid glands in phyllomedusine tree frogs, by providing a hydrophobic shield against terrestrial environs. They differ from the latter in that they are epithelial rather than syncytial in structure, undergo holocrine degeneration during lipogenesis and lack a myoepithelial sheath. Besides waterproofing the body surface and horny skin appendages (feathers and hairs), sebaceous units may play an accessory role as scent (odorous) glands, either as homogeneous secretory organs, or in association with apocrine sweat tubules (in mammals).

The smaller and more primitive lipogenic, secretory organs in reptilian skin consist of epidermal patches, "generation glands", including β- and escutcheon glands, which are anatomical traits used to track phylogenetic relationships among lizards (MADERSON and CHIU 1970; CHIU and MADERSON 1975; KLUGE 1983). Their histogenesis accompanies the processes of epidermis keratinisation and sloughing (QUAY 1972). Generation glands lack ducts and openings, a peculiar trait they share with the large lipogenic gland-bodies in the head skin of burrowing snakes of the genus *Typhlops* (BORGIOLI and LANZA 1986), and with the aggregations of lipogenic cells in the nucal skin of some Asian snakes (ELKAN 1972) and in the spiny tail skin of geckonids (ROSEMBERG and RUSSEL 1980; RICHARDSON and HINCHLIFE 1983). Nucal and tail organs have been regarded as glands merely on account of the ejecting mechanism, performed by skeletal muscles, which can squirt their fatty contents through epidermal "rupture zones". Actually, these organs lack any real secretory epithelial architecture and should properly be regarded as derivatives of mesodermal cells. Among the Squamata, several species

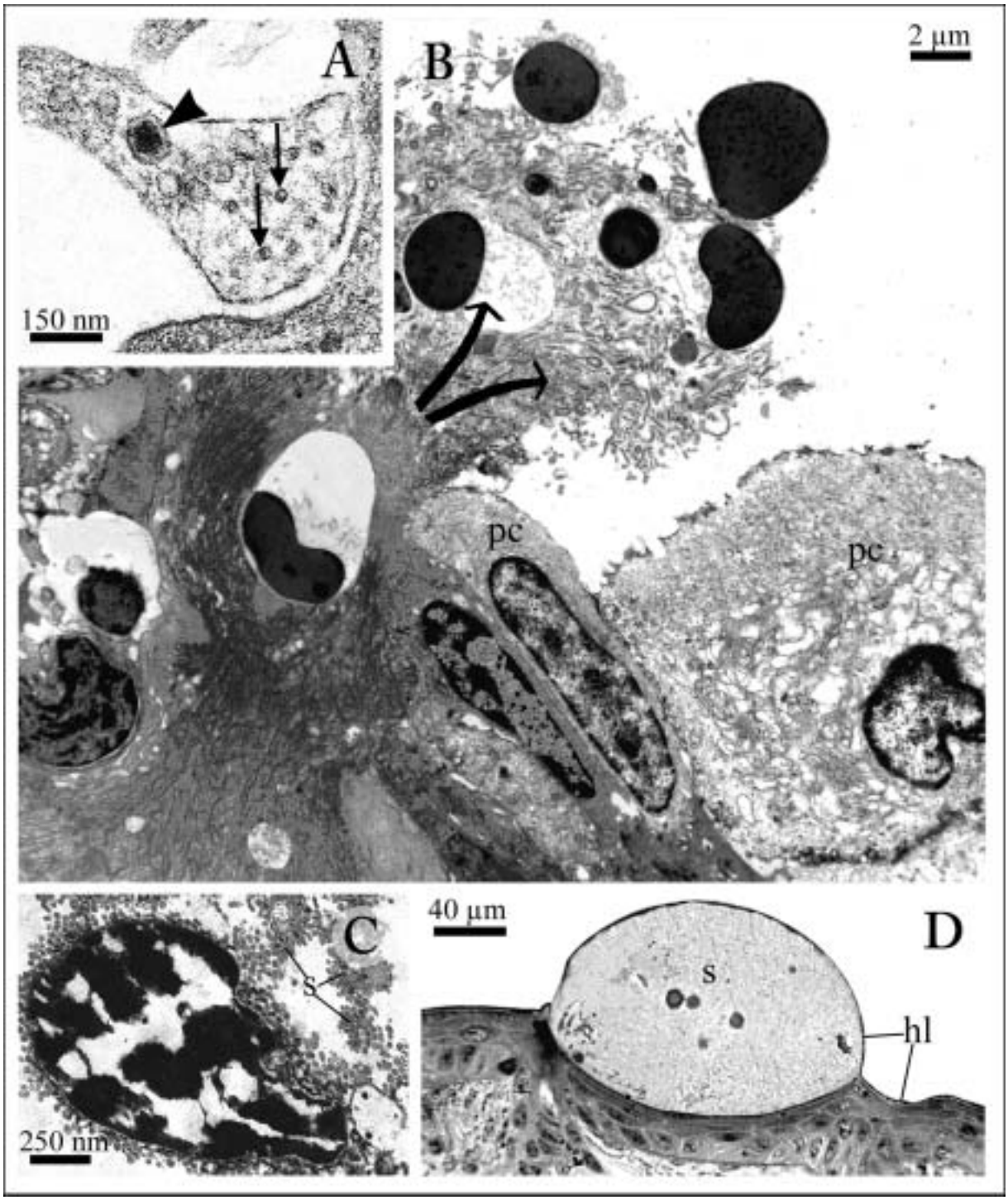

Fig. 4 — Functional patterns of anuran serous glands; A, B, C, transmission electron microscope; D, light microscope. A: Pre-metamorphic specimen of the black legged poison frog *Phyllobates bicolor,* adrenergic nerve ending in the secretory-contractile interstice, containing dense cored vesicles (arrowhead) and neurotubules (arrows). B: Serous gland in premetamorphic tadpole of the yellow-bellied toad (*Bombina pachyus*), during secretory discharge (bowed arrows) which involves dense granules and syncytial cytoplasm portions; notice external, peridermal cell (pc) typical of larval epidermis. C: *Hyla regilla* (the Pacific tree frog), nucleus of the syncytium collected with the secretory product (s) after discharge. D: *A. cisternasii* (juvenile specimen), during secretory discharge, the product (s) penetrates the interstices between epidermal cells lining the duct and becomes trapped below the horny layer (hl) on the skin surface.

possess real glands (i. e. provided with epithelial structure and duct), that are sometimes sexually dimorphic. These glands are topographically described as "preanal", "femoral" and "precloacal", and phylogenetically considered as putative specializations of the generation glands (MADERSON and CHIU 1970), which possibly represent vestigial organs (CHIU and MADERSON 1975). They arise from follicles invaginating into the dermis and usually maintain their follicular features, with an inner "secretory plug" that may consist of structureless cell debris (CHIU and MADERSON 1975) or fine granules (JARED *et al.* 1999), according to investigation methods. The epithelial follicle is surrounded by a thick connective tissue sheath; in larger femoral glands this emanates inner partitions, dividing the secretory parenchyma into tubes and tubules (COLE 1966a). Depending on the species, the plug material can vary in composition: lipids have been detected along with proteins, including keratins (COLE 1966b) and neutral mucopolysaccharides (ANTONIAZZI *et al.* 1993). Therefore some sebaceous-like glands are not exclusively lipogenic in nature, although their chemically heterogeneous, secretory material is produced according to the sebum manufacturing pattern, namely by stratified cells which undergo holocrine degeneration, starting from the periphery (ANTONIAZZI *et al.* 1993; 1994). Heterogeneous biosynthesis pathways and holocrine mechanisms are distinctive traits of chelonian mental, axillary and inguinal glands, involved in chemical defence and intraspecific communication (EHERENFELD and EHERENFELD 1973; QUAY 1986a).

Besides the holocrine lipogenic activity widely performed by epidermal cells, mainly in non-feathered areas of the skin surface (MENON *et al.* 1981), avian skin possesses small sebaceous-type glands and the conspicuous uropygial (preen or oil) gland (QUAY 1986b). In the chicken "rictus", epidermal cells undergo keratinisation and lipoidal degeneration, until a horny, multi-lamellar stratum, rich in oil droplets, covers the secretory layers. These lipogenic cell clusters resemble the simpler sebaceous glands in reptiles (where keratin accumulations overlie lipogenic cells) and anticipate uropygial organ features in their holocrine patterns (MENON *et al.* 1981). The preen gland exhibits common morphological, positional and functional traits in extant birds: it is an unpaired, usually bilobed structure, located dorsally in the caudal third of the synsacral bone, and involved in the production of an oily substance. Several aquatic species actively transfer this material to the plumage using their paddle-like beaks. The secretory units in uropygial glands consist of three cell layers (MENON *et al.* 1981): basal, intermediate and transitional (mature), foreshadowing a periphery-centre functional polarisation. Basal cells undergo mitotic processes, whereas enzymatic activities, involved in fat biosynthesis, occur in the other layers (JENIK *et al.* 1987). However, when features of secretory cytodifferentiation are considered, the intermediate and transitional layers can be ascribed to four stages of holocriny (WAGNER and BOORD 1975). Estrogens affect uropygial gland function: estriol treatment results in the suppression of its activity (MANNA *et al.* 1983), whereas estradiol enhances fatty acid diester biosynthesis, consistently with an increase in number of secretory cell peroxisomes (BOHNET *et al.* 1991). These organelles are involved in fat biosynthesis, as stressed by their close spatial relationships with paracrystalline clusters of smooth endoplasmic reticulum (SER) in preen gland adenocytes (FRINGES and GORGAS 1993).

Sebaceous glands "*sensu strictu*" are unique anatomical traits in mammalian skin. Apart from a few cases, in which these alveolar compound glands, involved in lipid manufacture, open directly onto the body surface, they are component parts of the pilo-sebaceous organs (Fig. 5B). In some instances, bundles of smooth muscle cells (*musculi arrectores pilorum*) are responsible for hair erection as well as secretory discharge from sebaceous glands (WELSCH *et al.* 1998; OZAKI *et al.* 2004). Therefore the anatomical relationship between hair follicles, sebaceous glands and arrector muscles of hairs assumes a full functional implication, summed up in the concept of a "follicular unit", involving the three anatomical component parts (POBLET *et al.* 2004). Since sebaceous glands arise with hairs from common Anlagen, their duct is continuous with the hair canal, where the sebum is released. However, this greasy product is not exclusively devoted to waterproofing hair, as the three-dimensional organization of the lipids on the skin is also involved in innate immune mechanisms and homeostatic functions (ZOUBOULIS 2004). Resembling hormone-producing organs, sebaceous glands are involved in steroidogenesis and androgen synthesis (ZOUBOULIS 2003; 2004). Different cell lines in the common pilo-sebaceous Anlage undergo divergent differentiation processes, lipogenic or keratogenic, respectively, through signalling pathways that include several products of Hedgehog genes (ALLEN *et al.* 2003; NIEMANN *et a*l. 2003). Investigations into the differential fates of these progenitor cells

involves transgenic mice, but experimental human models require immortalized sebocyte lines from human skin, since sebaceous gland development is extremely species-specific (ZOUBOULIS 2003). Studies on human immortalized sebocytes reveal that their terminal secretory differentiation is followed by apoptotic cell death (WRÓBEL *et al.* 2003). Sebaceous differentiation is inserted in a three-step, morphological sequence that *in vivo* characterizes: a) peripheral, b) intermediate, and c) inner cells (BELL 1986). Cells in these stages exhibit: *a*) typical features of an undifferentiated status (large amounts of free ribosomes); *b*) lipid biosynthesis (Golgi stacks and smooth endoplasmic reticulum, often in a thick aggregation; *c*) lipogenic (holocrine) degeneration. Along with other hormones, androgens are potent regulators of secretory activity in sebocytes, which during the terminal stage of differentiation are assisted by peroxisome proliferator-activated receptor ligands (ZOUBOULIS 2004).

Integration of histological and morphometric studies with ethological observations on ungulates, proved that specialized sebaceous glands are involved in olfactory and visual communication (TOSI *et al.* 1990). As already stated, sebaceous glands belong to the heterogeneous class of cutaneous scent organs (see below), either as exclusive secretory units or in association with sweat glands (QUAY 1986c).

Sweat glands - Mammalian skin annexa include one particular gland type, the sweat glands, which are tubular-coiled in shape and have a single-layered secretory epithelium (Fig. 5C) along with peculiar adenocyte features and release mechanisms. Apart from these morpho-functional traits, sweat glands share several structural features with amphibian cutaneous glands: i.e. the myoepithelial sheath, autonomic nerve supply and localised stem cell compartments involved in regeneration processes.

Secretory cells in sweat glands release their products either through a mechanism that under the LM is inconspicuous or by detachment of cell apices. Based on this criterion, eccrine and apocrine sweat glands are described. Eccrine glands, which are simple-tubular and open directly onto the skin surface, include two cell types: dark "mucoid" cells, involved in exocytosis of dense granules, and clear cells, which release intercellular fluids by producing ionic gradients via the Na^+, K^+ pump strategically placed in secretory and duct cell plasma membranes (HASHIMOTO *et al.* 1986). In these glands, only the dark cells perform a secretory function: eccrine tubules, which have sometimes been described with clear cells only should not therefore be considered real secretory organs (STUMPF *et al.* 2004). Apocrine glands are ramified-tubular with the common duct merging into the upper tract of the hair channel. During release, secretory cells leave behind large portions of their apices (aposomes), containing lysosomes and degenerated organelles, along with active molecules stored in the supra-nuclear cytoplasm.

These differential traits are basically common to sweat glands in all mammals and appear to be enhanced under conditions of stress which induce hyperactivity, such as hyperhidrosis (excessive sweating) in eccrine glands (BOVELL *et al.* 2001). However, some criticism has been raised about this synthetic classification of sweat glands. In eccrine glands, dense granules of dark cells contain large amounts of proteins, therefore these adenocytes should be properly described as "granular" (i. e. proteinaceous) rather than "mucous" or "mucoid" (SBARBATI *et al.* 1994). However, most proteins in dark cell granules are linked to saccharide moieties (including the sialic acid), to form a variable spectrum of neutral glycoproteins and sialoglycoproteins, involved in protecting the skin integrity from mechanical damages and microbial attacks (YASUI *et al.* 2005). The apocrine process has also been revised: whilst it is still regarded as a real, and not an artifactual secretory process (AUMULLER *et al.* 1999), both exocytosis and aposome detachment may occur in apocrine glands (WELSCH *et al.* 1998; STOECKELHUBER *et al.* 2003; YASUI *et al.* 2003; YASUI *et al.* 2004). Therefore, the attributes apocrine and eccrine lack any differential descriptive value, and the term monoptychic (namely, single-layered) should be adopted as a feature characterising both types of sweat glands (ZELLER and RICHTER 1990).

Myoepithelial cells in sweat glands derive from peripheral myoblasts in the fetal epidermal buds that have down-grown into the dermis (Fig. 5D). They are spindle shaped with their longer axis parallel to the secretory tubule, only partly ensheathed by the contractile layer (ELLIS 1965). They are absent around the intradermal duct, where poorly differentiated cells are arranged around the periphery of the inner cell layer. The myoepithelia of clustered apocrine glands in specific anatomical sites vary significantly in thickness, apparently fitting different densities of the secretory products in various regions of the cluster (OZAKI *et al.* 2004). In both types of sweat glands, mec_s are characterized by a conspicuous

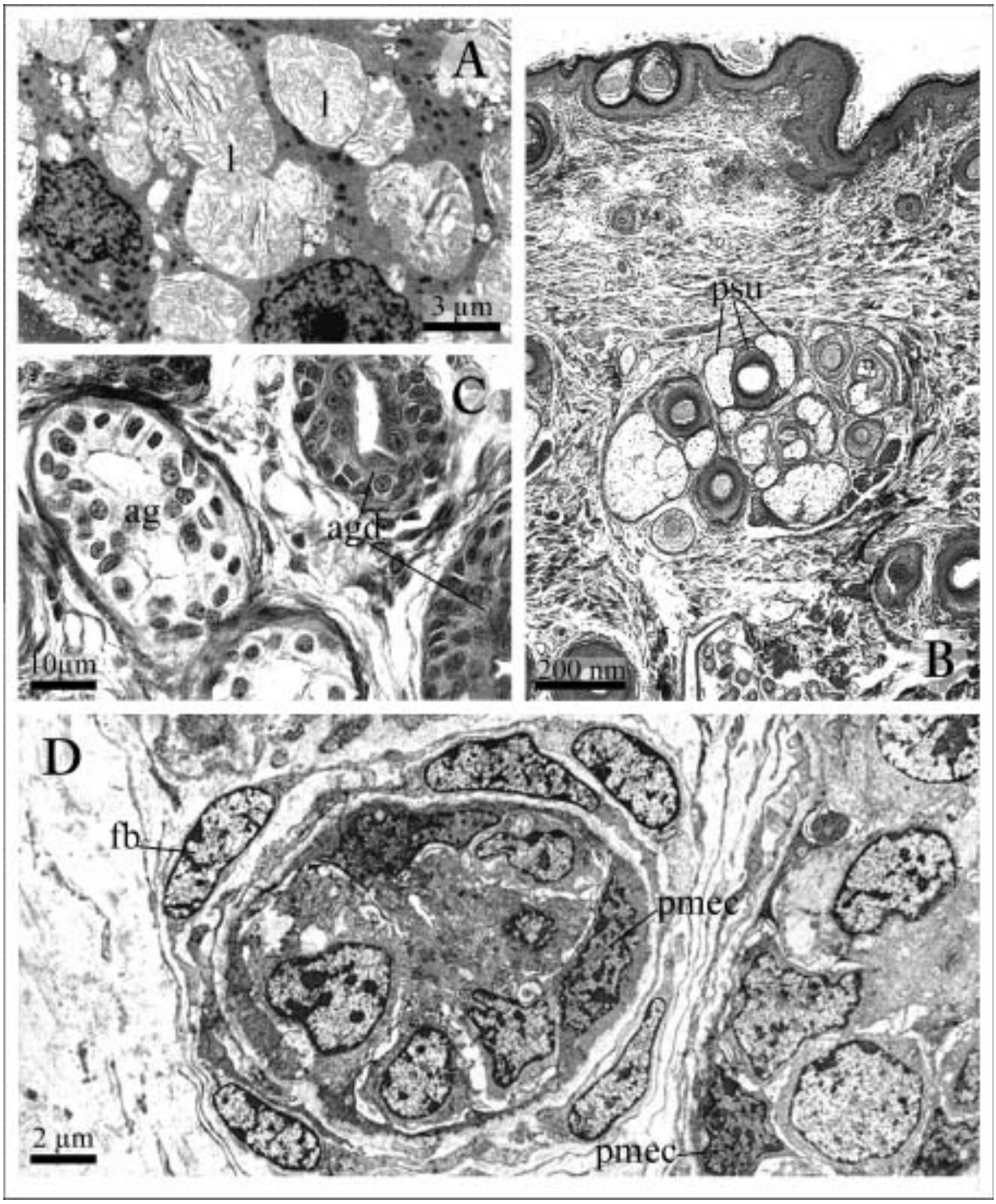

Fig. 5 — Lipid producing glands and sweat glands. A: *P. hypochondrialis* (adult frog), lipid deposits (l) in the secretory unit of a lipid gland (transmission electron microscope specimen). B: Pilo-sebaceous units (psu) in human skin under the light microscope, Mallory's triple stain. C: The same as above: apocrine gland (ag) and apocrine gland duct (agd). D: Transmission electron microscope patterns of sweat gland development in the metatarsal skin area of a wild boar (*Sus scrofa*) embryo; (fb = fibroblast), (pmec = presumptive myoepithelial cells).

cytoskeleton of dense bodies that allow attachment to actin myofilaments. Their end portions spread out into thin offshoots involved in neuromuscular junctions with autonomic nerve endings (FARNESI *et al.* 1999). Anatomically, this nerve supply is ortho-sympathetic in origin, but in eccrine glands it is pharmacologically cholinergic, rather than adrenergic as in the apocrine ones. Beside myoepithelial cells, the autonomic nerve endings also reach the secretory parenchyma, which may however perform intrinsic, autocrine regulation (ZANCARO *et al.* 1999).

In contrast to sebaceous glands, which have a peripheral/basal cell layer engaged in replacing dead adenocytes, sweat gland structure includes discrete stem compartments. Cells in these undifferentiated regions proliferate only slowly, but adequately enough to maintain a non-exhaustive secretory activity. Scattered adenoctytes in apocrine glands may be recycled several times (STOECKELHUBER *et al.* 2000) until they die and are replaced by differentiating secretory cells (ATOJI *et al.* 1998) that are still endowed with proliferative potentialities, depending on sex and/or age (STOECKELHUBER *et al.* 2000). This seems to occur in both types of sweat glands (MORIMOTO and SAGA 1995). However, proliferative activity in cells of the transitional duct tract is stronger than in adenocytes (STUMPF *et al.* 2004). Therefore the duct should be considered as the preferential site for hosting stem cells: adenoblasts (STUMPF and WELSCH 2002) and myoblasts (HAGIWARA and SHIBASAKI 1994).

Actually only human eccrine glands are sudoriparous in function, which means these organs, scattered throughout the skin, manufacture a watery product containing urea and are involved in both thermoregulation and excretion of nitrogen waste. Eccrine glands in non-human mammals are restricted to specific zones, such as the interdigital areas (LAMPS *et al.* 2001) or feet pads. In these sites, their watery product may prevent the feet from slipping on the substrate, provide defence against bacteria, assist in thermoregulation (STUMPF *et al.* 2004) and/or reduce and prevent physical damage to the skin (YASUI *et al.* 2005).

Apocrine glands are well represented in mammals, although in humans they occur in specific locations: the axilla, breast areola, ano-genital region, external acoustic canal (cerominous glands) and eyelid (Moll glands). Their viscous product contains odorous compounds that have characterized these glands as scent organs (see below). They form homogeneous clusters of apocrine secretory units or contribute to heterogeneous, exocrine clusters with sebaceous units (QUAY 1986c). Typical apocrine glands are targets for androgens whereas specialized Moll glands in humans and higher primates lack both androgen and estrogen receptors (STOECKELHUBER *et al.* 2003; 2004). On the other hand, human apocrine axillary glands produce volatile steroids (ROTHARDT and BEIER 2001), usually released as pheromones by scent glands (see below). However, these molecules acquire a typical odour once processed by aerobic diphteroid bacteria in the local microbial flora of skin (DOWNING 1986; STOECKELHUBER *et al.* 2003).

Ceruminous and Moll glands share common traits with ordinary apocrine glands, but they are specialized in function, since their products contain glycoconiugates (glycoproteins and, possibly, proteoglycans) which contribute to antimicrobial defence. These glycoconiugates protect the anterior eye chamber with the contribution of mucins from various origins (corneal and conjunctival epithelial cells, lacrimal glands and goblet cells, STOECKELHUBER *et* al. 2003), and the external ear channel, in association with sebaceous gland products (YASUI *et al.* 2003; YASUI *et al.* 2004), respectively. The antimicrobial activity results from several saccharide residues of the glycoconiugates which have been also found in ordinary cutaneous apocrine glands of the common seal (MEYER *et al.* 2000). Furthermore, immunohistochemical methods also detected a variety of antimicrobial proteins in the secretory products of Moll glands (STOECKELHUBER *et al.* 2004).

Cutaneous scent glands - As previously stated, integumentary glands proper, involved in chemical (scent or odorous) communication, belong to the sebaceous or apocrine types, or include secretory units of both the former types (QUAY 1986c). The role of cutaneous secretions in signalling between co-specific individuals is, however, more complex in mammals: in ungulates it includes a repertoire of behaviours, acting together with visual signs, such as vigorous rubbing of the horns against the substratum, to deposit sebaceous products from the supraoccipital glands (TOSI *et al.* 1990). The clustering of apocrine and sebaceous glands in specific cutaneous localizations is sufficient to suggest that they are scent organs, although secretory units of both types usually also coexist in not-specialised, hairy skin areas. The secretions from the two different gland types may be functionally integrated on the release areas. Sebum is the putative carrier of scent molecules (STOECKELHUBER *et al.* 2000), acting as a long-lasting preservative of

odorous products released by apocrine glands in a rapidly evaporating medium (WELSCH *et al.* 1998). In addition, both products easily adhere to the environmental substrata (OZAKI *et al.* 2004). Scent products include glycogoniugates (WELSCH *et al.* 1998) as well as steroidal compounds (STOECKELHUBER *et al.* 2000) that also occur in human axillary apocrine glands (ROTHARDT and BEIER 2001). Usually secretory units of either type form separated layers in scent glands, reflecting the levels they occupy in non-specialized skin. So, the sebaceous organs are more superficial while the apocrine glands are located in the deeper skin layers (HELDER and FREYMULLER 1995; ATOJI *et al.* 1998; WELSCH *et al.* 1998; STOECKELHUBER *et al.* 2000, figs1a and 2a; OZAKI *et al.* 2004, figs 2a and 2b).

Based on the data summarized above, an appropriate attempt to devise a comprehensive system for classifying the diversity of cutaneous scent glands in mammals should consider: a) the kind/s of component secretory units (sebaceous and/or sweat apocrine), b) the relative size of each part in "mixed" scent organs, c) the type and degree of secretory specialization of such units and d) the specific functional roles. Unfortunately, current classification is based merely on simple anatomical location, which means it provides no information on any possible homologies, namely phylogenetic and/or ontogenetic relationships between homonymous glands in different areas, or indeed heteronymous glands in identical areas (QUAY 1986c).

CONCLUSIONS

In the frame of a phylogenetic survey, the evolutionary trends of secretory cell lines in the skin of vertebrates reveals a close relationship with changes in the habits of these organisms, according to the boundary role of the cutaneous apparatus between the internal and external environments. The evolutionary pathway of secretory cell lines in the skin is marked by two milestones which correspond to: a) the transition from the aquatic to the subaerial environs, b) the integral adaptation to terrestrial life.

In the former adaptive stage, single mother cells of the mucous and serous lines undergo cloning and, possibly, early differentiation processes in the epidermal microenvironment, and segregate into the dermis as complex organs. Along with the usual dichotomy between mucous and proteinaceous lines, multicellular glands in amphibians reflect the taxonomy of extant Lyssamphibia. The consistent differences in serous gland features between the anuran order, on the one hand, and urodeles and apodans, on the other, confirm diversity in specialized cells of larval skin, and support the hypothesis that two phylogenetic lines gave rise to modern amphibians.

However, no cutaneous gland type in extant amphibians can be considered ancestral of the lipid producing (sebaceous-like) glands in Reptilia, which represent the cutaneous secretory novelty accompanying advanced colonisation of the subaerial environment. Although no information is available on skin glands from fossil records of amphibian ancestors of Amniota (Antrachosauria), it appears that extensive skin keratinisation during phylogenesis contrasted the development of serous and mucous glands, while lipogenic evolution of specific epidermal areas accompanied the development of horny cell layers.

According to a possible phylogenetic scenario involving mammalian-like reptiles (order Therapsida), the thin patches of epidermis alternating with to horny scales should give rise to pilo-sebaceous units and associated apocrine sweat glands. Indeed, the *quinconce* pattern shown by ancestral hairs (bristles) during mammalian development reflects the alternating distribution of non-keratinized skin areas between the horny scales. It is possible that eccrine sweat glands appeared later in mammalian evolution, accompanying the development of the diffuse, modern thin hairs after the loss of reptilian scales. Despite any asynchrony in their development, apocrine and eccrine sweat glands share several common traits with amphibian cutaneous glands, whilst they differ noticeably from the contiguous sebaceous glands. However, the wide phylogenetic gap between amphibians and mammalians, and the possible effects of convergent evolution, call for caution in interpreting these similarities. Even if we by-pass diversities in their shape, a relevant difference can be observed between amphibian cutaneouos glands and sweat glands: the loss of dichotomy between the proteinaceous and mucous lines in both the eccrine and aprocrine secretory units. Whereas ordinary secretory cells in apocrine sweat glands as well as the dark cells in eccrine glands produce apparently proteinaceous granules, and can be referred to the serous type, mammalian skin lacks mucous glands, i.e. secretory organs producing mucopolysaccharides (glycosoaminoglycans) destined to form foamy secretory masses. Actually, apocrine gland adenocytes as well as dark cells in eccrine glands exhibit the biosynthetic capabilities found

in both serous and mucous lines, since they produce granules containing proteins, glycoproteins, glycosoaminoglycans and steroids. Therefore, it seems that a single secretory cell type exists in mammalian sweat glands, which holds together the biosynthetic traits of distinct cutaneous glands in lower vertebrates.

Further adaptive pressures (ranging from thermo-regulation to waste excretion) led to the differentiation of clear cells in eccrine sweat glands, specialized in transmembrane ion transport. These cells, rich in mitochondria, are representative of an ancient specialized line in the epidermis of vertebrates, including the ionocytes, that allow the euryhaline bony fishes to survive in a relatively wide environmental salinity range. Whether clear cells in sweat glands be derivatives of ionocytes or the result of convergent evolution in non- closely related taxa, they nevertheless emphasise the adaptive flexibility of specialized epidermal cells in vertebrate skin.

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