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The Harderian gland, its secretory duct and porphyrin content in the mongolian gerbil (*Meriones unguiculatus*)

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INTRODUCTION

The Harderian gland occurs in most terrestrial vertebrates as an orbital structure associated with the nictitating membrane (Walls, 1942; Bellairs & Boyd, 1947; Sakai, 1981). It has received much attention in recent years as a potential site of immune response (Mueller, Sato & Glick, 1971; Albini, Wick, Rose & Orlans, 1974; Burns, 1979); as part of a retinal–pineal axis (Wetterberg, Geller & Yuwiler, 1970; Wetterberg *et al.* 1970) and as a source of (*a*) pheromones and/or (*b*) thermoregulatory lipids. The last two postulated functions have been extensively studied (Thiessen, Clancy & Goodwin, 1976; Thiessen & Rice, 1976; Thiessen & Kittrell, 1980; Thiessen, Pendergrass & Harriman, 1982) in the mongolian gerbil (*Meriones unguiculatus*) yet there is no widely available account of the structure of the gland in this species. The present study was undertaken to provide a description of the gland and its duct and to quantify one of its products – porphyrin (characteristic of rodent Harderian glands).

MATERIALS AND METHODS

The animals used were 20 male and 14 female adult gerbils of agouti coat colour. Animals were killed after sodium pentabarbitone anaesthesia and allocated to one of three groups:

(i) Animals (six males and four females) in which both glands were immersed in 5 % glutaraldehyde and processed for transmission electron microscopy; two additional males were used which had been perfused with 5 % glutaraldehyde by ventricular perfusion.

(ii) Animals (eight males and seven females) in which one gland was fixed in Bouin's fluid for light microscopy and the other assayed for porphyrin content using a total porphyrin extraction routine.

(iii) Animals (four males and three females) in which both glands were used for the determination of different forms of porphyrin using high pressure liquid chromatography.

Techniques

Electron microscopy

Glands were fixed in phosphate-buffered glutaraldehyde (pH 7·2–7·5) for 3–4 hours, rinsed in several changes of phosphate buffer and then post-fixed in 1 % osmium tetroxide (phosphate-buffered to pH 7·2–7·4) for 3–6 hours. Further rinsing in buffer

was followed by dehydration through ascending grades of ethanol (the 70% stage containing 5% uranyl acetate for enhanced contrast and cellular detail). Tissues were finally cleared in propylene oxide and embedded in Araldite resin mixture.

Survey semithin sections (0·5–1·5 μm thick) were cut on a Reichert Autocut and stained by azur blue II. Localised areas were selected and thin sections cut on an L.K.B. ultratome. Grids with thin sections were stained with uranyl acetate solution followed by lead citrate solution (Reynolds, 1963). Sections were examined in a Jeol 100S transmission electron microscope.

Light microscopy

Glands were fixed in Bouin's fixative for 24–36 hours and dehydrated in the usual manner for wax embedding. Serial sections, 5 μm in thickness, were taken through each gland and an interrupted series of one section in 25 was mounted and stained with haematoxylin and eosin.

Total porphyrin extraction

Glands were extracted with 95:5 methanol:hydrochloric acid until no further fluorescence could be detected in the solvent. The total volume was noted and 1 ml taken and diluted with 9 ml 1·5 N hydrochloric acid. The solution was read on a spectrofluorimeter against a coproporphyrin standard.

Analysis of porphyrin types

Gland porphyrins were assayed by high pressure liquid chromatography according to the method of A. Seubert and S. Seubert (personal communication, method to be published).

RESULTS

General appearance

The Harderian gland of the gerbil is crescent-shaped (with the attachment to the nictitating membrane on its convex border), black-brown in colour, and is the largest orbital structure. The mean weights of paired glands were 188 ± 30 (male) and 199 ± 15 (female) mg per 100 g body weight. There was no statistically significant sex difference in weight. The gross intraorbital relationships of the gland have been described previously in *Meriones unguiculatus* (Brownscheidle, 1974) and *M. meridianus* (Sakai & Yohro, 1981).

The pattern of lobulation and branching of secretory ducts in Harderian glands is a subject of controversy (Sakai, 1981) and it was not the intention of the present study to examine this aspect. Nevertheless it was noted that, after removal from the orbit, glands exhibited three lobes; a major and minor lobe, one on each side of the

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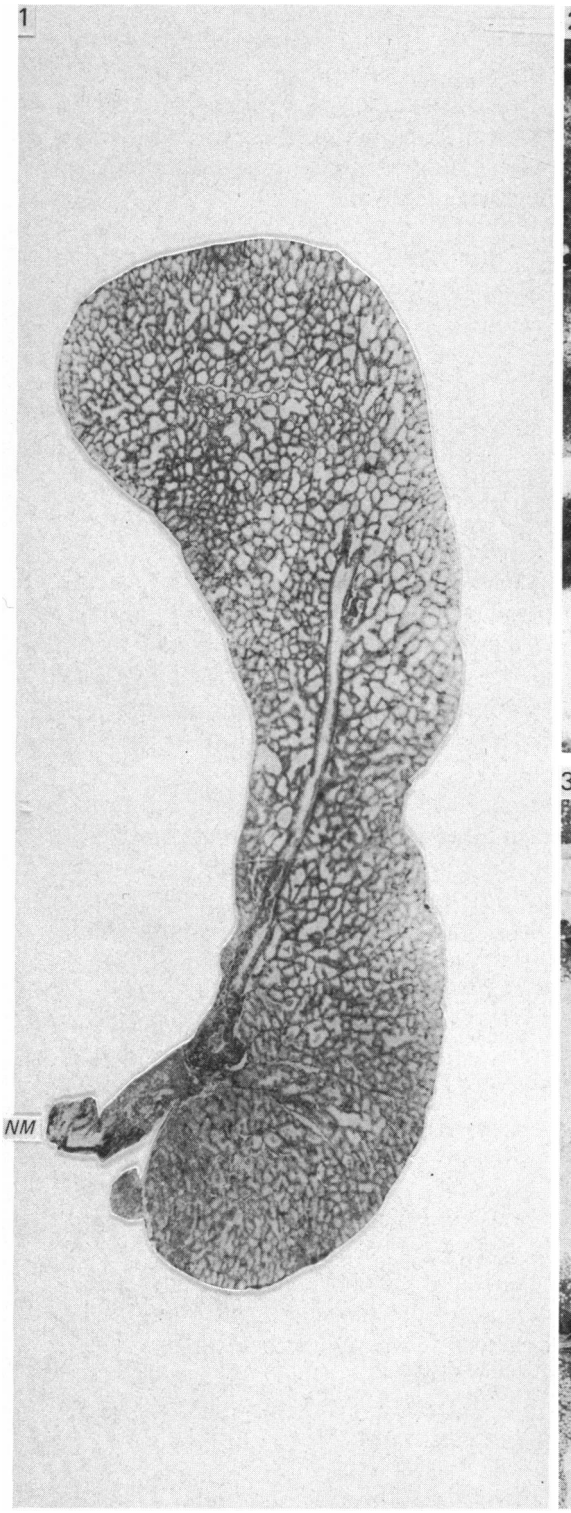
Fig. 1. A low power view of a longitudinal section through the gerbil Harderian gland showing its association with the nictitating membrane (*NM*). Conspicuous features are (i) the numerous tubular profiles and (ii) a main lobar or lobular duct continuous with the extraglandular secretory duct. × 17.

Fig. 2. Several gland tubules may be seen, some of which contain solid intraluminal accretions composed of lipids and porphyrin. × 300.

Fig. 3. A portion of a major intraglandular duct surrounded by connective tissue, vessels and gland tubules. Within the gland the duct is lined by a single layer of normal tubule cells. Its wide lumen is filled with lipid vacuoles. × 500.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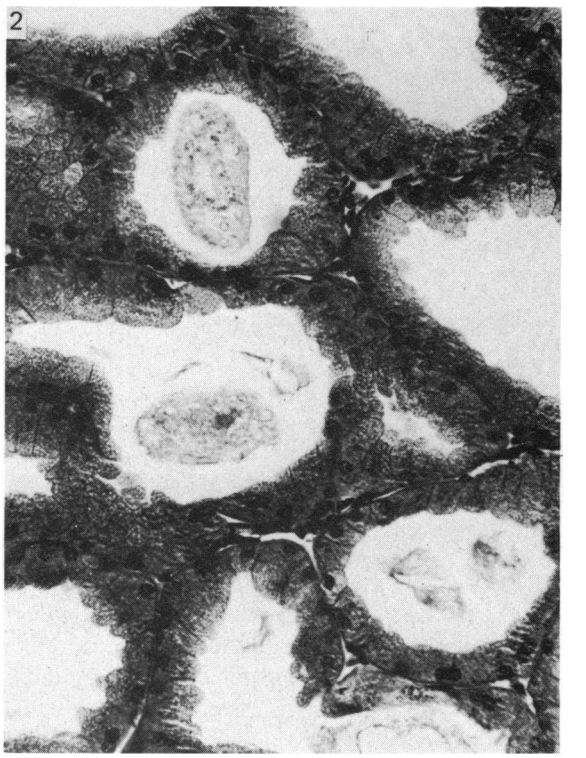
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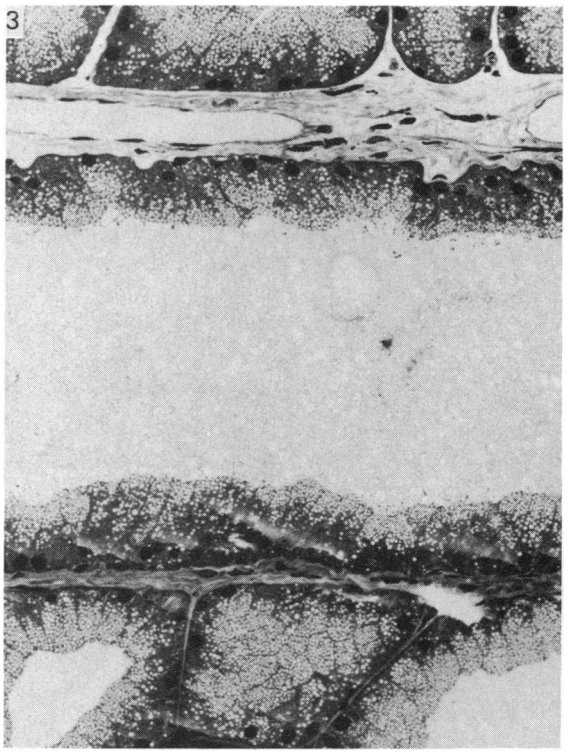
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attachment to the nictitating membrane and a small pyramidal lobe lying between them opposite the attachment. Each lobe showed clear evidence of further subdivision into lobules. Light microscopy (Figs. 1, 3) occasionally revealed a long straight portion of intraglandular secretory duct which was continuous with the extraglandular duct. It was composed of typical glandular epithelium and of comparatively wide diameter. These portions were filled with lipid vacuoles and cellular debris and must have represented main lobular or lobar ducts.

Gland histology and ultrastructure

A description of the gland cells may be conveniently divided into three parts – gland tubules, interstitial cells and the gland duct.

(*A*) *Gland tubules*

Within the substance of the gland, the tubule walls (Fig. 2) were normally composed of gland epithelium and myoepithelial cells; occasionally, tubules were composed of extraglandular ductal epithelium.

(i) *Gland epithelium*

This consisted of columnar cells (Fig. 4) whose apices frequently bulged into the lumen of the tubule. Their lateral and basal plasma membranes showed interdigitations, particularly where the basal plasma membrane overlay a myoepithelial cell. Junctional complexes were inconspicuous. The apical membrane projected as small slender microvilli except in areas where secretory vacuoles bulged from the cell; where a vacuole had recently been released, a smooth concavity was left in the cell surface (Fig. 5).

The nucleus was large, spherical, basally located and contained prominent nucleoli and considerable amounts of heterochromatin. Gland cells were frequently binucleate. Granular endoplasmic reticulum was present usually as an accumulation surrounding the nucleus and often showed continuity with the nuclear envelope (Fig. 7). Rosettes of ribosomes were also abundant around the nucleus. Small amounts of granular endoplasmic reticulum and rosettes occurred randomly elsewhere throughout the cytoplasm. Large areas of cytoplasm were filled with small vesicle-like structures, which were very closely packed and thus gave the cytoplasm a particularly dense opaque texture. These were thought to be elements of the smooth endoplasmic reticulum. No typical Golgi complexes were observed in the gland cells. However, the cells contained one or more small vacuoles which may have represented Golgi structures. Mitochondria were numerous but not conspicuous, and were seen as round or elongated structures with dense matrices and irregularly spaced cristae.

The apical half of each cell was almost wholly occupied by secretory lipid vacuoles (Fig. 5) whose maximum diameter reached 2 μm: scattered secretory vacuoles were also present in the mid- and basal parts of the cell. A condensation of electron-dense material was sometimes seen coating the inside of the vacuole membrane or as an amorphous deposit within the vacuole. There was little evidence of coalescence of vacuoles, and vacuoles appeared to be secreted from the cell by exocytosis. While this may have been the most common form of secretion, holocrine shedding of cells also occurred (Fig. 6) and nuclear and cytoplasmic debris were often seen in the wider diameter tubules.

One of the most striking features of the gland cells was the presence of myriads of randomly orientated cytoplasmic 'slashes', which were of uniform width and up

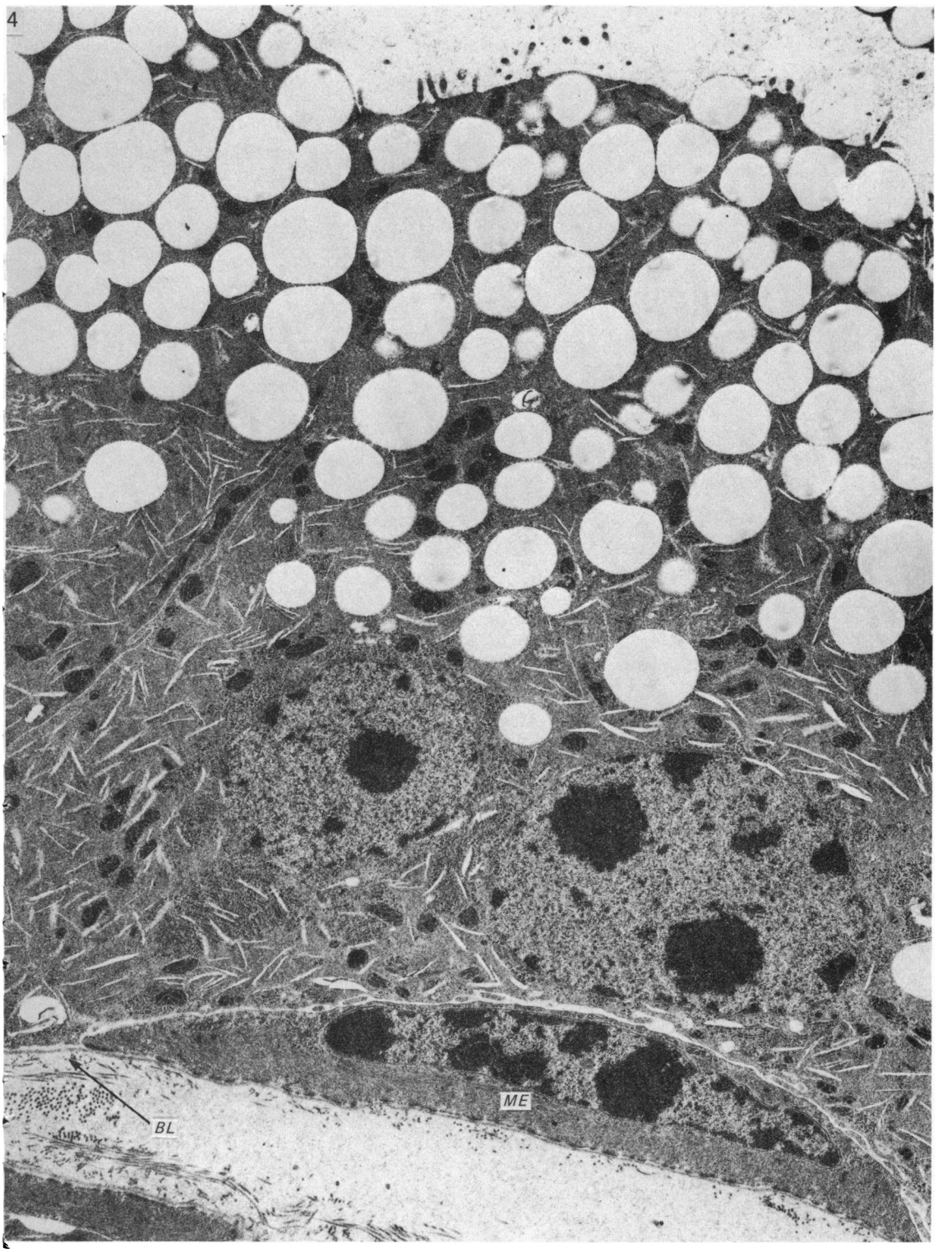
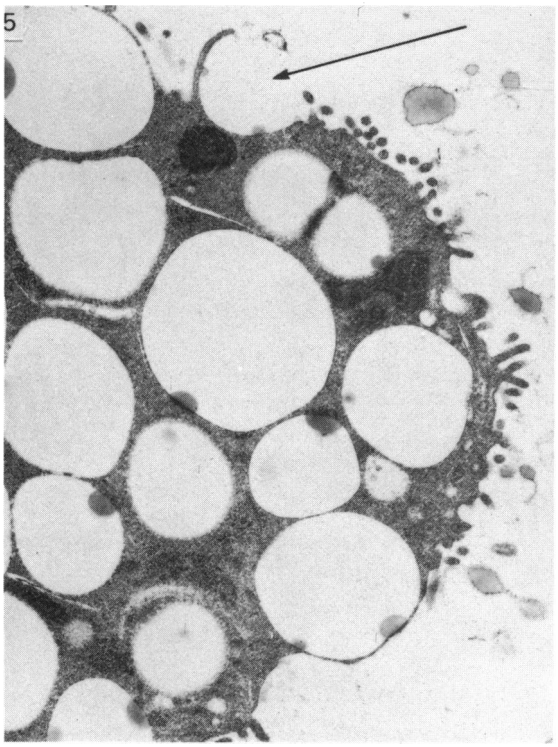
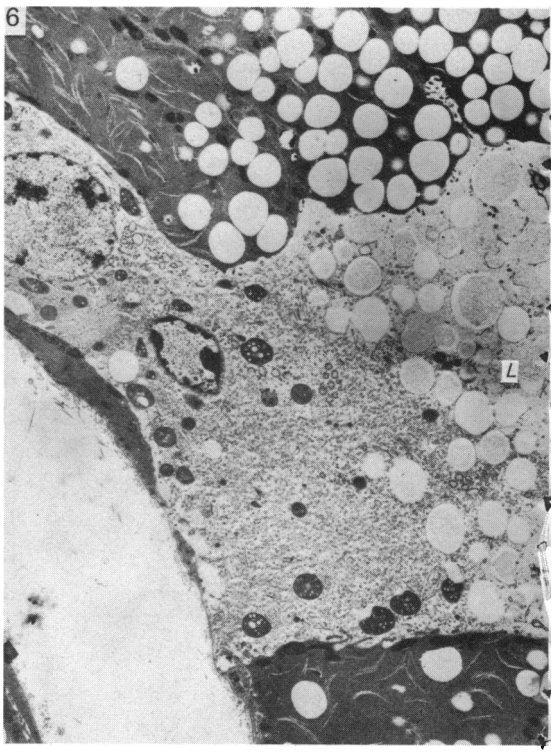


Fig. 4. A Harderian gland tubule epithelial cell. Conspicuous features are (i) the numerous cytoplasmic 'slashes' and (ii) the lipid vacuoles occupying the apical half of the cell. Although most cells are uninucleate, binucleate cells (as in this example) are frequently encountered. The cell rests on a myoepithelial cell (*ME*) contained within its basal lamina (*BL*). × 8150.

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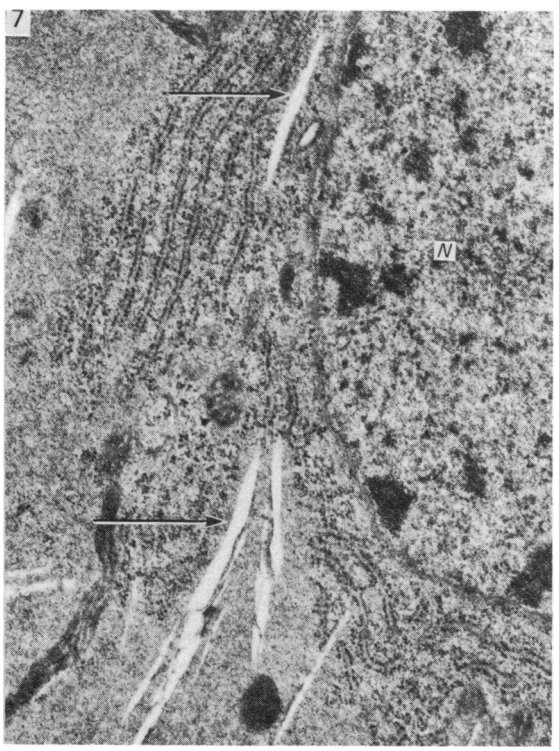
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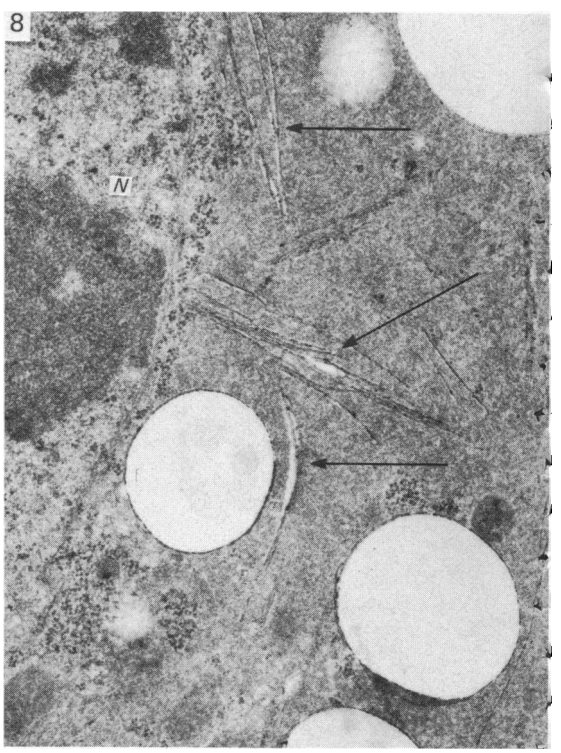
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to approximately 1·5 μm in length (Fig. 7). Frequently, a 'slash' contained a strand or membrane of very dense material, usually lying to one side. In some cells of some gerbils examined, large numbers of very dense cytoplasmic membranes were found. They were usually seen as pairs of straight or slightly curved densely osmiophilic parallel but unconnected lines (Fig. 8). Some of these membrane pairs showed regions where they were apparently associated with an expanded area resembling a cytoplasmic 'slash', suggesting they may have been precursors of the latter.

(ii) *Myoepithelial cells*

The gland tubules were surrounded by a meshwork of myoepithelial cells lying within the basal lamina (Fig. 4). They were narrow and elongated with the myofilaments running along the long axis of the cell. Cells which were apparently in contraction showed a corrugated profile. The cytoplasm apposed to the basal lamina exhibited hemidesmosomes.

(iii) *Ductal islets*

Small isolated pockets of extraglandular ductal tissue occurred within the glands of some animals. These are described below with the duct itself.

(*B*) *Interstitial cells*

As well as the normal components of connective tissue such as fibroblasts, collagen, blood vessels, etc. the following elements were notably present.

(i) *Melanocytes*

Melanocytes (Fig. 9) were very numerous in the interstices of the gerbil Harderian gland and rendered the gland a dark brown/grey colour. They were generally located in the wider interstices but their attenuated cytoplasmic extensions occurred throughout the gland.

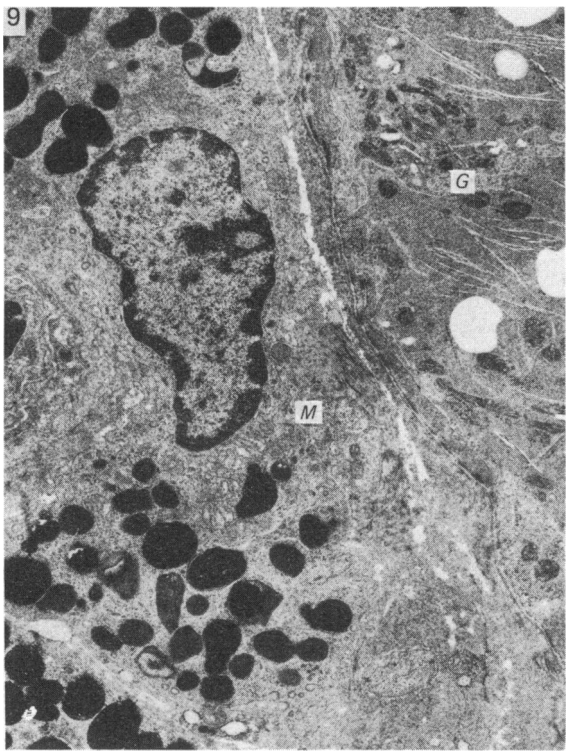
They varied in shape, having a prominent nucleus and dilated cisternae of granular endoplasmic reticulum. Their granules were of medium electron density and of variable size and shape (for example, round, elongated and club-shaped) and most of them contained a second mature granule of much greater electron density and considerable physical hardness, as judged by the difficulty in obtaining sections without artefactual cutting 'chatter'. Only mature spherical melanin granules were observed in the cytoplasmic extensions. No helicoidal structure, typical of melanosomes in many other species, was observed.

Fig. 5. The apical region of a tubule cell showing microvilli and lipid vacuoles. A partly extruded vacuole (arrowed) may be seen. × 12500.

Fig. 6. An example of holocrine secretion. Two tubule cells (or a binucleate cell) are seen discharging into the lumen (*L*). × 5000.

Fig. 7. An area of tubule cell showing cytoplasmic 'slashes' (arrowed). There is a conspicuous corona of rough endoplasmic reticulum surrounding the nucleus (*N*). × 20000.

Fig. 8. An area of tubule cell showing dense membranous couplets (arrowed) some of which exhibit putative 'slash'-precursors. A nucleus (*N*) and lipid vacuoles can be seen. The lower vacuoles are lined by dense amorphous material. × 22000.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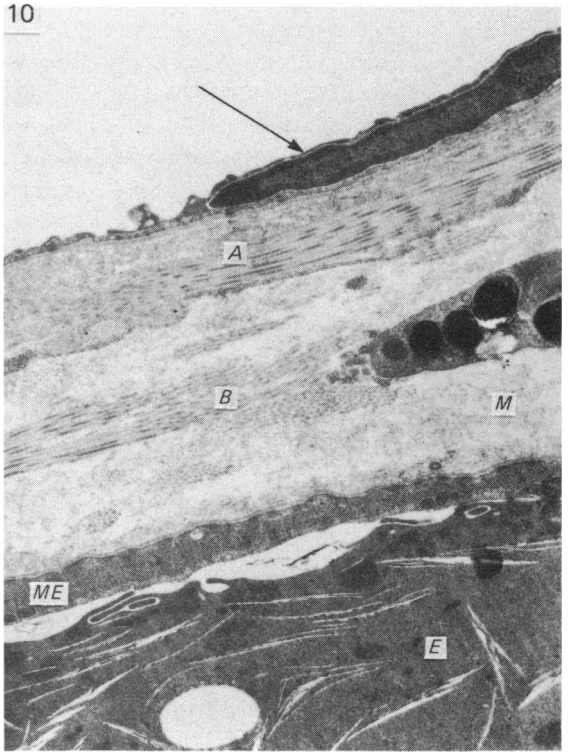
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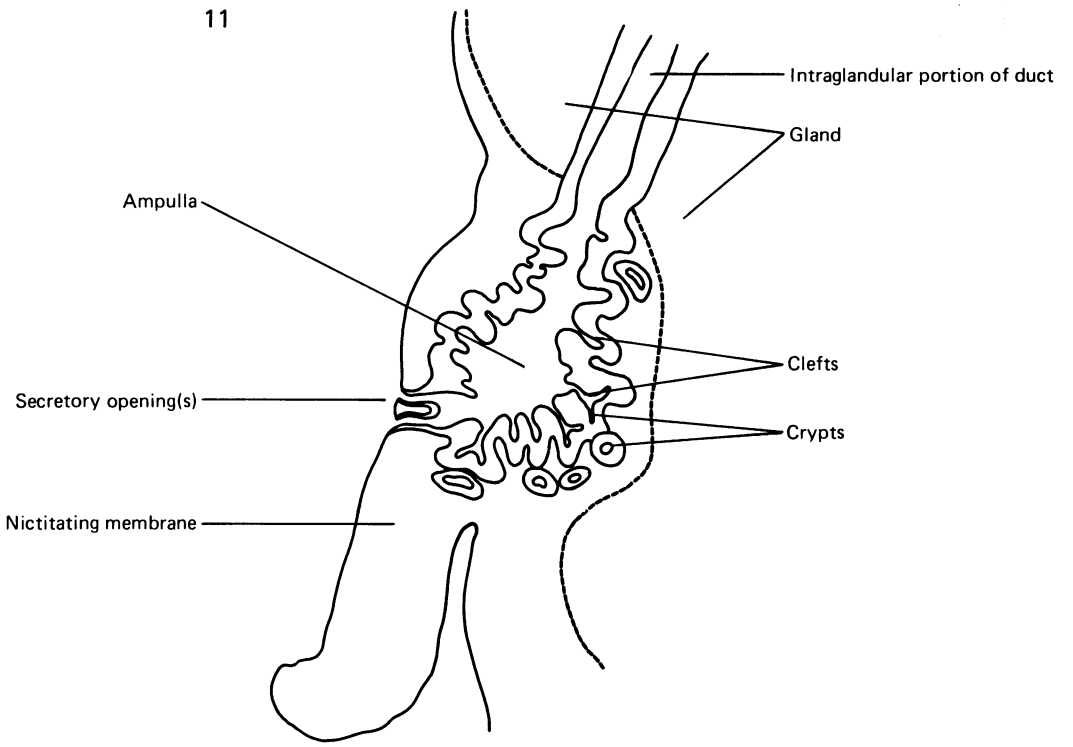
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Intraglandular portion of duct
Gland
Ampulla
Clefts
Secretory opening(s)
Crypts
Nictitating membrane

(ii) *Other cells*

Mast cells occurred frequently in the interstitial areas of the gland. They resembled mast cells of other rodents and were generally packed with granules. Plasma cells were numerous throughout the interstitial area. Macrophages and eosinophils were occasionally found. In addition, many myelinated and unmyelinated nerve fibres were seen. Some fibres lay very close to myoepithelial cells but no junctions were observed.

(iii) *Connective tissue of capsule (Fig. 10)*

The capsule was said by Sakai & Yohro (1981) to represent the wall of an orbital venous sinus. Immediately outside the glandular tissue there was a layer of sparse collagen fibres containing cell types such as fibroblasts, melanocytes and mast cells. Beyond this lay a denser acellular layer composed entirely of regular packed collagen fibres. Surrounding this was a final external layer of cells resembling endothelium with remarkably attenuated cytoplasm (becoming as thin as 0·1 μm in places), resting on a basal lamina and bearing frequent small irregular projections.

(*C*) *Harderian gland secretory duct*

Long straight portions of secretory duct occurred within the body of the gland (Fig. 1) and were lined by a single layer of typical tubule cells (Fig. 3). The extraglandular portion of the secretory duct had a bulbous dilatation or ampulla, the walls of which were thrown into simple folds; between these folds were narrow clefts, some of which ran down into crypts (Fig. 11).

From the ampulla, the secretory duct narrowed again to open on to the nasal surface of the nictitating membrane. Sometimes it branched to give two openings at the surface.

(1) *Ampulla of secretory duct*

There were three cell types in the epithelium lining the ampulla of the secretory duct.

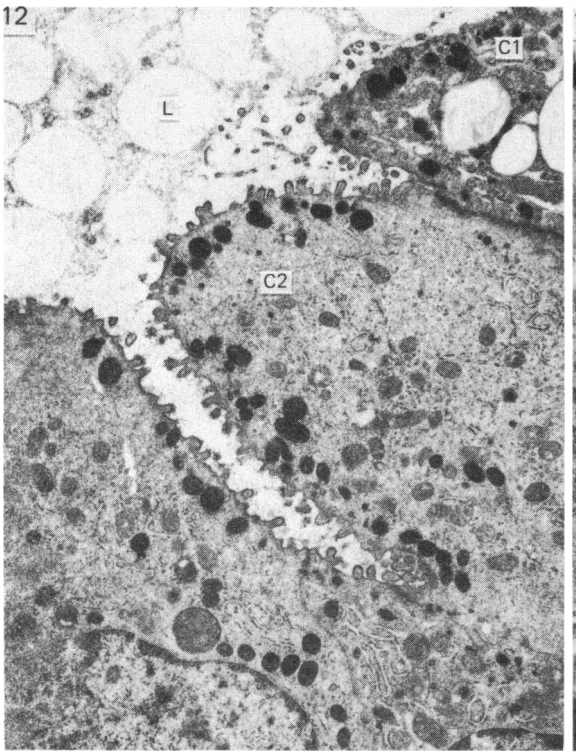
(i) Low columnar or cuboidal cells (Fig. 12) were similar to tubule cells but showed two differences. Firstly, the frequency and size range of the lipid vacuoles was more variable than in the tubule cells, for example, some cells contained only a few large lipid vacuoles. Secondly, in addition to lipid, the cells contained numerous small dense apical granules. These cells were situated on the crest of the folds.

(ii) Lining the walls of the clefts were cuboidal cells which possessed small dense granules in the apical part of the cell but no lipid vacuoles. Their luminal surface was covered with small stubby microvilli (Fig. 13).

Fig. 9. An interstitial melanocyte (*M*) lying close to a gland tubule (*G*) and containing granules of varying size, shape and density. × 7000.

Fig. 10. The outer capsule of the Harderian gland showing (i) part of a highly attenuated surface cell (arrowed), (ii) an outer acellular layer of regular collagen fibres (*A*) and (iii) an inner layer of loose cellular connective tissue (*B*) in which part of a melanocyte (*M*) may be seen. A myoepithelial cell (*ME*) and epithelial cell (*E*) of a gland tubule appear in the lower part of the micrograph. × 11000.

Fig. 11. A diagram of the arrangement of the intra- and extraglandular portions of the Harderian gland secretory duct in the gerbil.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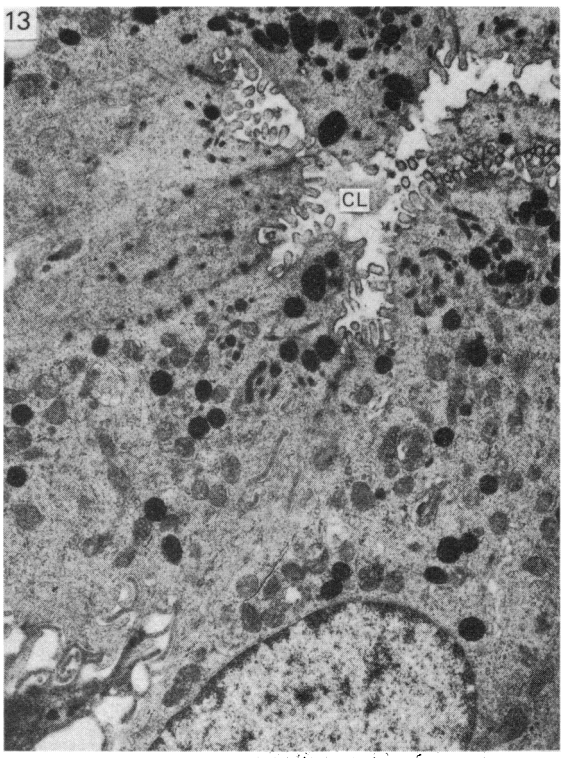
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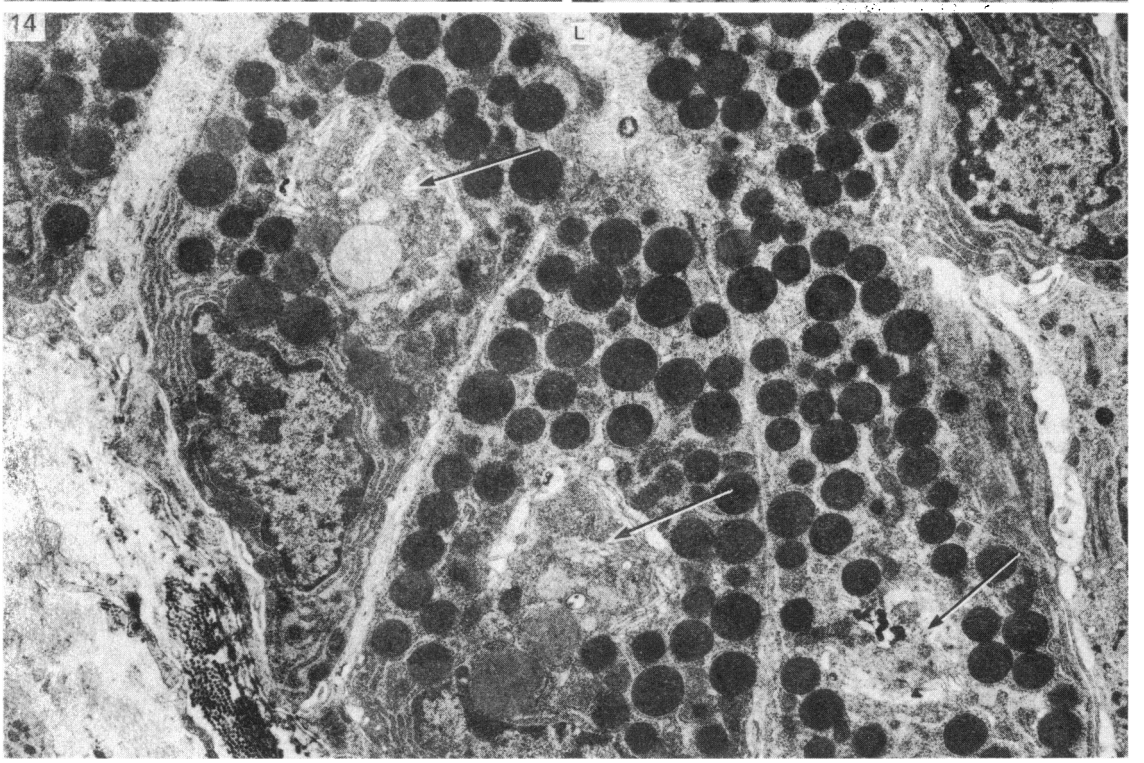
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(iii) The crypts were lined by low columnar cells with basally situated nuclei. The remainder of the cell was packed with dense granules (Fig. 14), which were much larger and more regular in shape than those in the cleft cells. Basally, there was extensive granular endoplasmic reticulum with large cisternae. The Golgi complex was well developed and occupied a supranuclear position. Within the Golgi complex were numerous granules of different size and density suggesting different stages of maturation. The apical surface of the cell was covered with slender filamentous microvilli. There were no myoepithelial cells surrounding the crypts.

(2) *Crystalloid bodies*

In some deep clefts (often at the junction with the crypt), aggregations of geometrically-shaped structures of varying sizes were observed (Fig. 15). At higher magnifications a regularly laminated sub-unit, with a 7·6 nm periodicity, was resolved within many of the structures depending on their orientation. The bodies were found only within the cleft lumen, and never within any of the cells lining either the clefts or the deeper crypts.

(3) *Opening of secretory duct*

As the duct emerged on to the nictitating membrane its surface was smooth and its epithelium contained two cell types (Fig. 16). (i) Cells which were very similar to the second ductal type present in the ampulla had a scattering of small dense apical granules and surfaces bearing very short microvilli. These cells were more flattened than those in the ampulla. (ii) The second type was a distinctive goblet-shaped cell with a narrow apex and a broader base. It was packed with dense secretory granules, seen being secreted in clumps onto the surface of the duct opening.

(4) *Ductal islets*

Small pockets of ductal tissue occurred within the body of the gland in some animals. Some were close to the main secretory duct, others at the gland periphery. They contained cells similar to the crypt cells of the duct ampulla, and crystalloid bodies were frequently observed. Tubule profiles were noted occasionally in which ductal cells and normal tubule cells appeared together. This suggested that the pockets of ductal tissue were not wholly isolated from the normal gland.

Porphyrin content

High pressure liquid chromatography determinations (Fig. 17) revealed that three out of the four male and two out of the three female glands contained only protoporphyrin. One animal of each sex possessed small amounts of coproporphyrin. Total porphyrin content of female glands (213 ± 69 nmol/g) reached higher levels than male glands (89 ± 35 nmol/g) but the difference was not statistically significant

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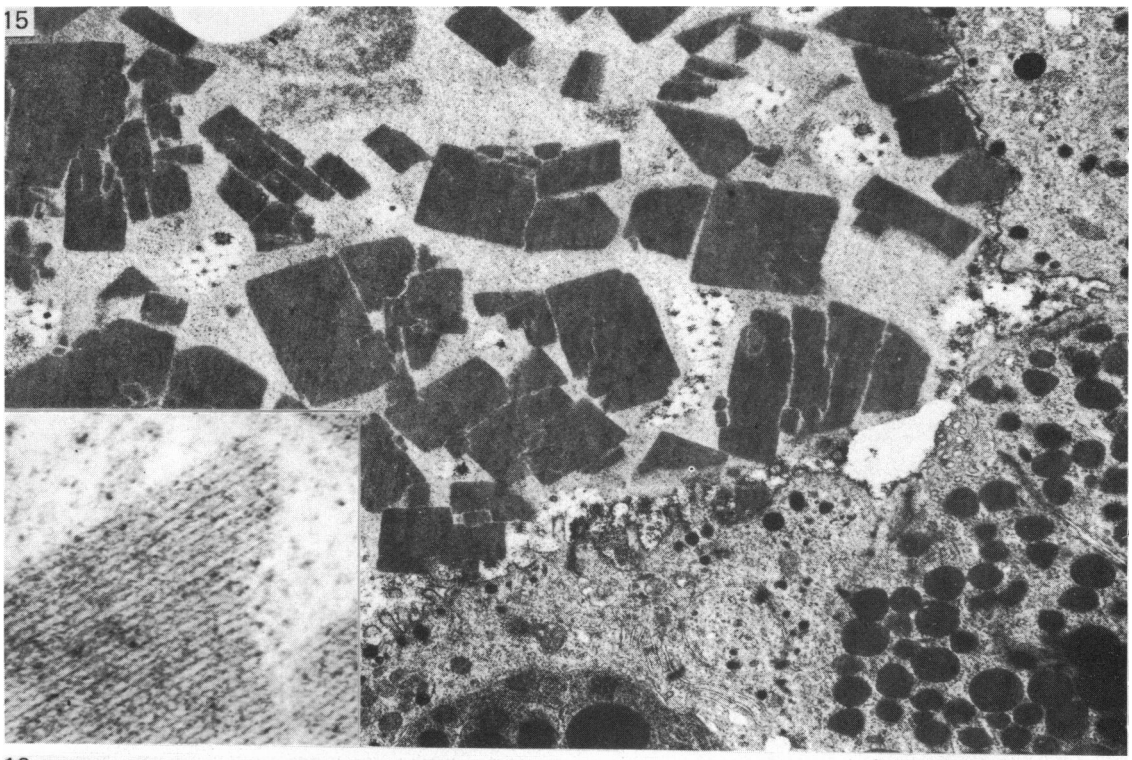
Fig. 12. Cells lining the wall of the ampulla. Some cells (C1) resemble tubule epithelial cells in possessing lipid vacuoles; others (C2) do not. Both types exhibit small dense apical granules and bear stubby microvilli. The ampullary lumen (L) contains lipid vacuoles and cellular debris. × 8000.

Fig. 13. A length of ampullary cleft (CL) lined by cells identical to C2 in Fig. 12. × 9000.

Fig. 14. A crypt cut transversely showing a narrow lumen (L) and serous lining cells. The latter contain numerous large dense granules and possess conspicuously active Golgi regions (arrowed). × 7000.



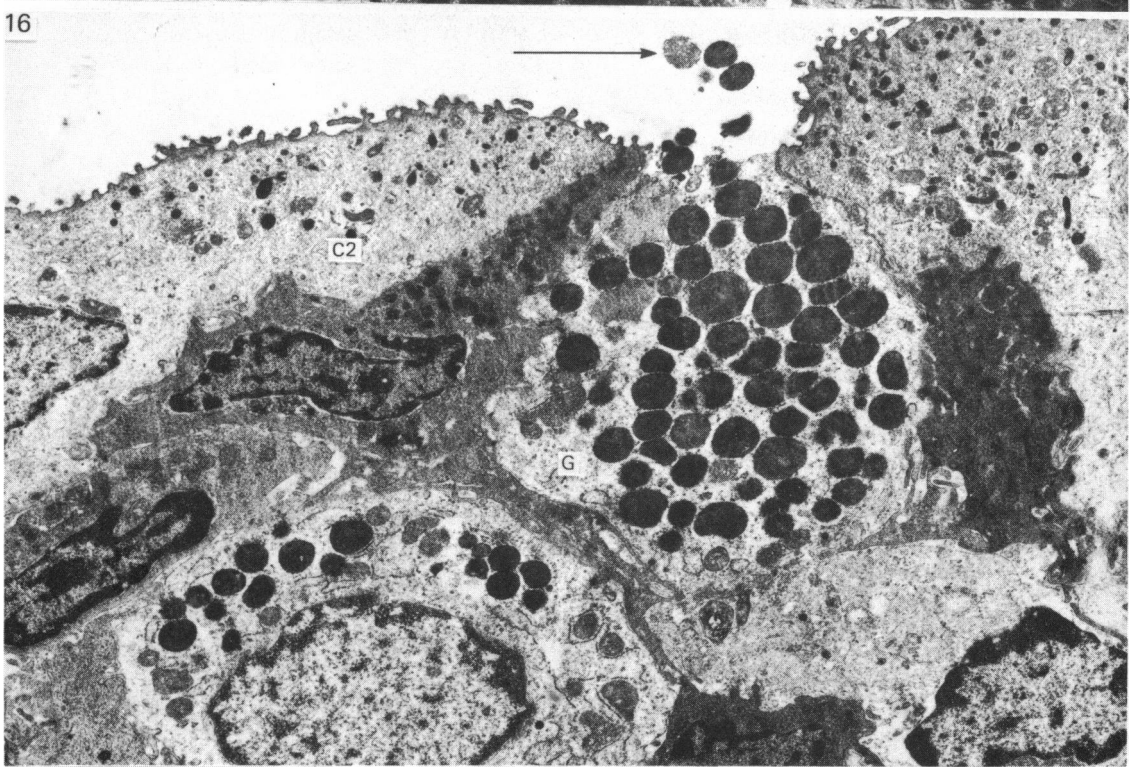


Fig. 15. Crystalloid bodies within the lumen of a cleft–crypt junction. These exhibit a range of sizes and geometric shapes. × 11 500. *Inset*: Higher magnification of an area of a crystalloid body showing its regular layered structure. × 175 000.

Fig. 16. The wall of the secretory duct near its opening onto the surface of the nictitating membrane. Here the ampullary type C2 cells are almost squamous (compare Fig. 12) and there are conspicuous goblet cells (G) secreting mucoid granules (arrowed) into the lumen. × 5250.

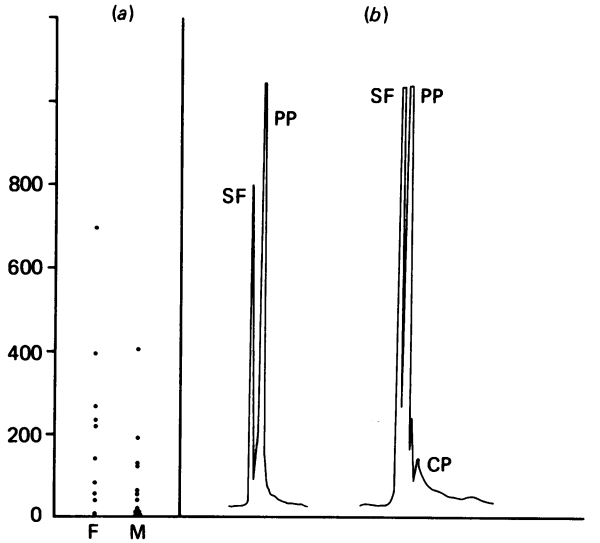


Fig. 17. (*a*) Porphyrin levels (expressed as nmol/g) in the Harderian glands of female (F) and male (M) gerbils. (*b*) Representative high pressure liquid chromatography traces of gerbil Harderian gland porphyrins. Both traces show the solvent front (SF) and protoporphyrin (PP) peaks. The right hand trace shows an additional minor coproporphyrin (CP) peak.

($t = 1{\cdot}78$, D.F. $= 20$, $P < 0{\cdot}10$). Solid intraluminal accretions of porphyrin (Fig. 2) were sparse; furthermore, some solid accretions did not fluoresce red under ultraviolet illumination, implying that they had a low porphyrin content. Since many accretions were filled with lipid vacuoles, there may have been considerable variability in the proportions of lipid : porphyrin making up the solid intraluminal deposits.

DISCUSSION

This description of the Harderian gland in the gerbil (*Meriones unguiculatus*) accords well with reports of other rodent species. Thus, the gland tubules are lined by a single layer of columnar cells which bear apical microvilli, contain lipid secretory vacuoles, have a basally located nucleus (and are frequently binucleate) and are surrounded by myoepithelial cells, as in the mouse (Woodhouse & Rhodin, 1963), the rat (Orban & Kelenyi, 1962; Brownscheidle & Niewenhuis, 1978), the golden hamster (Bucana & Nadakavukaren, 1972), and in the rabbit (Bjorkman, Nicander & Schantz, 1960). In rats, mice and male hamsters, two kinds of tubule cells are found. This is not the case in the gerbil, nor in the closely related *Meriones meridianus* (Sakai & Yohro, 1981) nor in the female hamster. Morphological sex differences abound in the hamster Harderian gland (Christensen & Dam, 1953; Payne *et al.* 1982) but do not occur in other species; none have been found in the present study. The gerbil also resembles other rodents in that the gland contains porphyrins. These are both detectable chemically and visible as solid intraluminal accretions which fluoresce red under ultraviolet illumination. The glands of female gerbils have a slightly higher porphyrin content than those of males; sex differences in porphyrin content have been noted in the hamster (Payne, McGadey, Moore & Thompson, 1977; Hoffman, 1971) and mouse (Shirama *et al.* 1981) and may represent the norm for rodents.

Although the Harderian glands of different rodent species share many common features, none are identical. This is well illustrated by comparisons of the present findings with a recent report on the closely related *M. meridianus* (Sakai & Yohro, 1981). While there are many similarities between the two species, the tubule cells of *M. meridianus* totally lack the cytoplasmic 'slashes' so characteristic of *M. unguiculatus*. It is unlikely that these are fixation artefacts. They occur in both immersion- and perfusion-fixed glands and in all tubule cells. Other ultrastructural features (and other cells) appear normal. Furthermore, they have been described independently in a study of *M. unguiculatus* by Brownscheidle (1974). Again, solid intraluminal accretions of porphyrin (so typical of rodent Harderian glands) are said not to occur in *M. meridianus* but do so in *M. unguiculatus*. Specialisations shared by the two species include, firstly, the presence in the interstitium of melanocytes which render the gland grey-black in colour and, secondly, the occurrence of islets of ductal tissue within the body of the gland. The islets have been described previously by Sakai (1981) as ectopic lacrimal glands but there is little evidence for this view.

The most unusual and characteristic feature of the tubule cells in *M. unguiculatus* is the presence of the cytoplasmic 'slashes'. While these are not membrane-bound, electron-dense material frequently occurs within the slash. It is thought that slashes may be related to the dense cytoplasmic membrane pairs or couplets which occurred in some of the animals. The size, distribution and random orientation of the slashes correspond closely to that of the membranous couplets; furthermore, transitional stages between couplet and slash are observed. Indeed, the membranous couplets may represent a stage in the formation of the numerous lipid-filled vacuoles, with the cytoplasmic slashes as an intermediate structure. Like the slashes, it has not proved possible to resolve a unit membrane delimiting the vacuole except where it becomes apparent near the cell apex. In addition, thin deposits of amorphous material (such as occur within slashes) frequently line vacuoles. Similar findings have been reported for *M. meridianus* (Sakai & Yohro, 1981). Vacuoles display remarkable uniformity of shape and size, partially formed vacuoles not being apparent. There is no evidence for a localised source of vacuole formation within the cell.

Finally, it is interesting that the gland secretion (normally considered to consist of lipids and porphyrins) may be augmented by serous and mucous secretions produced by cells of the duct. This should be taken into account when interpreting studies of the possible role of the Harderian gland in pheromone production (Thiessen, Clancy & Goodwin, 1976; Thiessen & Rice, 1976).

SUMMARY

The Harderian gland, its secretory duct and porphyrin content were examined in the mongolian gerbil (*Meriones unguiculatus*). The gland consisted of tubules lined by a single layer of epithelial cells and a myoepithelial network. The tubule cells were often binucleate and possessed lipid vacuoles in the apical half of the cell, a corona of granular endoplasmic reticulum surrounding the nucleus, and cytoplasmic 'slashes'. The latter are probably derived from dense membranous couplets and may be precursors of the lipid vacuoles. Holocrine and merocrine secretion was observed. Interstitial cells included plasma cells, mast cells and (predominantly) melanocytes which render the gland black. The gland was surrounded by a collagen capsule and an outer layer of highly attenuated (possibly endothelioid) cells. Within the gland, the secretory duct was lined by a single layer of normal tubule cells. Outside the gland,

the duct enlarged to form an ampulla, from which clefts led off to deep crypts. The ampulla and clefts were lined by cells with small dense apical granules and stubby microvilli; some possessed lipid vacuoles. The crypts were lined by serous cells with active Golgi regions. At the duct opening, ampullary cells became squamous and goblet cells occurred. Geometric crystalloid deposits (with a layered structure of 7·6 nm periodicity) occurred at cleft–crypt junctions. Islets of extra-glandular ductal tissue were occasionally found within the gland. Porphyrins were detectable both by chemical assay and fluorescence microscopy. There was a trend for female glands to have a higher content than males. Solid intraluminal accretions of porphyrin and/or lipid were present.

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