ANNALS OF ANATOMY

Bilateral dimorphism of Loewenthal's gland in young male albino rats: an ultrastructural investigation

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Summary. This study represents a further contribution to our knowledge about the structure of Loewenthal's gland. There are several divergences in the available literature on the topic, concerning both the histological and ultrastructural findings. However, in these studies, the authors did not take into account the potential influence of a putative side-dependent dimorphism previously reported by us. We therefore carried out histological and electronmicroscopic observations specifically aimed at evaluating the importance of the gland shape for its structure. In particular, in male albino rats aged 70–120 days, we compared the structure of the left and right glands. Depending on the side undergoing morphological investigation, we observed differences in the acini, cells, nuclei, endoplasmic reticulum, Golgi apparatus and granular content. Apart from slight individual differences, we found that structural variations were most frequently observed in glands displaying a more evident macroscopic side-specific dimorphism. Our findings demonstrate that several conflicting data in the literature dealing with the structure of Loewenthal's glands might be explained by the morphofunctional side-dependent dimorphism of the organ.

Key words: Loewenthal's gland – Bilateral dimorphism – Histology – Ultrastructure – Male rat

Introduction

About hundred years ago, Loewenthal (1895, 1899) first discovered and described, in the rat, a gland located at the base of the ear, near the parotid. This gland, which represents one of two lobes of the lacrimal gland, shifts towards the parotid during ontogenesis; Loewenthal therefore called it the "sus-parotid". Later, other authors defined this organ as "Loewenthal's" gland, or the "exorbital lacrimal", "extraorbital", "external orbital", "iuxta-parotid" or "pre-parotid" gland, reporting more detailed morphological and structural data (Greene 1935; Venable and Graffin 1940; Teir 1944).

This gland was histologically described as "sero-acinar" by Walker (1958), Baquiche (1959), Martinazzi and Turolla (1961), Ichikawa and Nakajima (1962), Martinazzi (1962, 1963), Casasco and Osculati (1967) and "seromucous" by Scott and Pease (1959), Bignardi and Aureli (1962), Quintarelli and Dellovo (1965), Essner (1971) and Sashima et al (1989).

Other authors reported a sexual dimorphism (Gabe 1955; Parhon et al. 1957; Walker 1958; Baquiche 1959) describing several features, such as acinar size, cell border, nuclear volume and morphology. Subsequently, sex-related differences were also observed, connected with variations in the DNA and RNA content, number of nucleoli and vesicles, connective tissue area, protein or glycoprotein levels and enzyme activity (Cavallero 1967; Paulini et al. 1972 a, b; Sullivan et al. 1984). Age-dependent acinar variations, consisting of vacuolizations and lipid acinar inclusions, were also observed; these changes were more evident in male rats (Sashima et al. 1989), and represented a typical feature of Harder's gland. As a result, Walker (1958) and subsequently Coujard and Coujard (1974), termed this phenomenon "harderization". The various studies differ as regards the time of onset and the entity of both sexual dimorphism and harderization of the gland.

Several studies included the use of biochemical and immunocytochemical analyses in order to relate the physiol-

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ogy of the gland function to the composition of the lacrimal fluid. Heterogeneous material was found in its secretions, such as tyrosine, histidine, tryptophan, cysteine (Martinazzi 1962, 1963), porphyrins (Bignardi Aureli 1962), leucine aminopeptidase activity (Lauria and Porcelli 1979) calcium (Roomans 1984), immunoglobulins (Gudmundsson et al. 1985) and prolactin (Mircheff et al. 1992). In addition, other functional proteins were found within the gland, such as endogenous peroxidase (Essner 1971), carbonic anhydrase isozymes (Hennigar et al. 1983), androgen receptors (Ota et al. 1986), a pH-sensitive anion exchanger (Lambert et al. 1991) and Na^+, K(+)-ATPase (Okami et al. 1992).

On the other hand, ultrastructural work on the rat exorbital lacrimal gland provided detailed, even spatially restricted, data about the gland structure (Scott and Pease 1959; Leeson 1960; Ichikawa and Nakajima 1962; Casasco and Osculati 1967; Luciano 1967; Alexander et al. 1973).

In a previous morphological study (Ricciardi et al. 1994) we also reported a macroscopic bilateral dimorphism. In particular, the gland of one side appears ellipsoidal in shape, often with a clearly visible peduncle, in comparison with the roundish or oval and thicker controlateral one. The present work aims to make a detailed study, using histological and ultrastructural techniques, of the glands of both sides, carrying out a comparative analysis on young male albino rats.

Materials and methods

Forty male albino rats (Wistar stock) 70, 80, 90, 100 and 120 days old, were used throughout the study. After delivery to our laboratory, the animals were housed in a controlled room, under a 12-hour light/12-hour dark cycle at 22–24 °C, with 50–60% relative humidity, and were sacrificed after at least two weeks of environmental adaptation; they received a standard laboratory diet and tap water *ad libitum*. Rats were sacrificed by intraperitoneal injection of an overdose of chloral hydrate (400 µl/100 g b. w.) and both exorbital glands were immediately removed, quickly examined from a macroscopic point of view, and then quartered.

For transmission electron microscopic examination, little blocks (about 5 mm^3) taken from corresponding areas (near the apex of each gland) were fixed with aldehyde solution (3% glutaraldehyde in 0.1 M phosphate buffer, pH 7.2) for 90 min, post-fixed in 1% buffered OsO_4 for 2 h and embedded in Epon-araldite. Ultrathin sections, obtained with a LKB ultramicrotome, were subsequently stained with uranyl acetate and lead citrate. Observations were made under a Jeol JEM 100 SX electron microscope.

The remaining part of each gland was fixed in saline formalin or Bouin's fluid and then processed for paraffin embedding. Finally, serial sections (7 µm) obtained were stained with haematoxylin and eosin (H/E), periodic acid-Schiff (PAS/H), toluidine blue, and Gomori's and Goldner's methods, and were subjected to light microscopy.

Numerical data relating to the areas of acini and cells were analyzed by means of an image analyzer (Leitz ASM 68 K) equipped with a light microscope, and a Q basic program for automatic image analysis. By using this procedure we measured the areas of acini and cells of ten sections belonging to each age group. Statistical evaluations were performed by the GraphPAD InStat version 1.15 program, using Student's t test for unpaired data; $p < 0.05$ was considered significant.

Results

In young Wistar rats, we found a clearly visible macroscopic bilateral dimorphism. Indeed, the gland of one

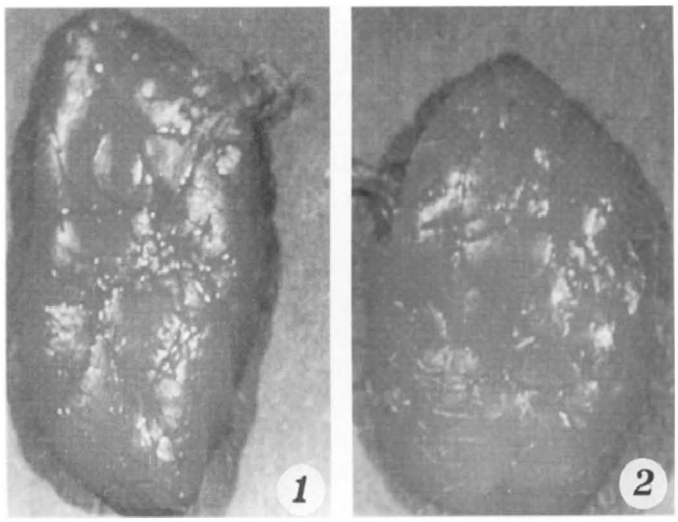


Fig. 1. Lateral view of ellipsoidal gland of 120-day-old rat. ×6.5
Fig. 2. Lateral view of roundish gland of 120-day-old rat. ×6.5

▶

Fig. 3. Ellipsoidal gland cell of 70-day-old rat. Rough endoplasmic reticulum (RER), well-developed with dilated cisternae (arrow). Numerous clear (c) and less clear (lc) non-homogeneous granules. Note the half-moon-shaped nucleus (n) close to a vacuole (v), Golgi apparatus (arrow-head). ×7 800

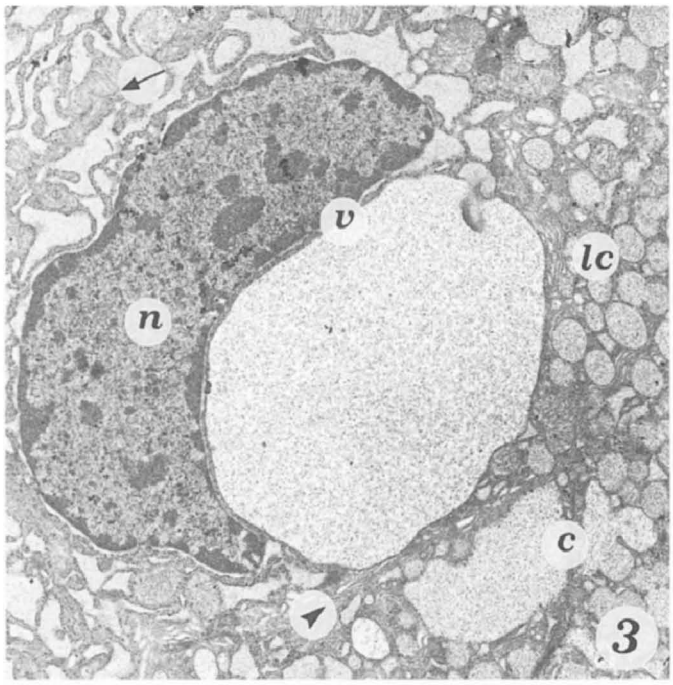
Fig. 4. Roundish gland cells of 70-day-old rat. RER sponge-like (arrows), a nucleus with a wavy envelope (n), scattered clear (c) and less clear (lc) non-homogeneous granules and vacuoles (v). On right lower side, portion of cell with closely-packed cisternae of RER (arrow-head). ×5 300

Fig. 5. Ellipsoidal gland cells of 80-day-old rat. RER with parallel (arrow) and dilated cisternae (arrow-head), nucleus (n) and clear non-homogeneous granules (c). ×8 400

Fig. 6. Roundish gland cells of 80-day-old rat. RER dilated cisternae (arrow), clear (c), less clear (lc), dark granules (d) and nucleus (n). ×6 000

Fig. 7. Cell portion with lipid-like structures (arrow) and lipid droplets (arrow-heads). ×5 200

Fig. 8. Histological section of roundish gland of 80-day-old rat. Note variation in shape and size of the nuclei, some of them giant (arrows). ×450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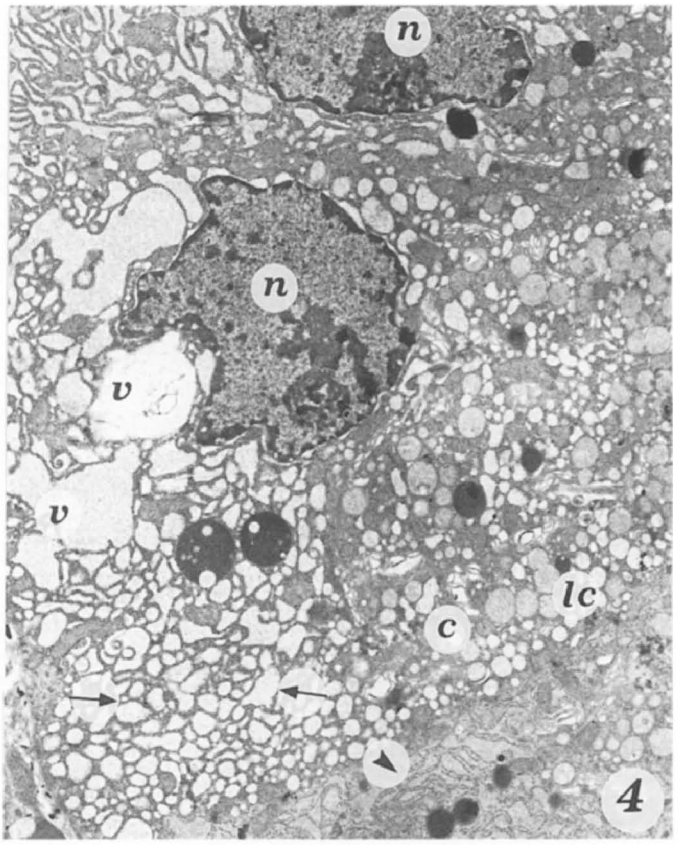
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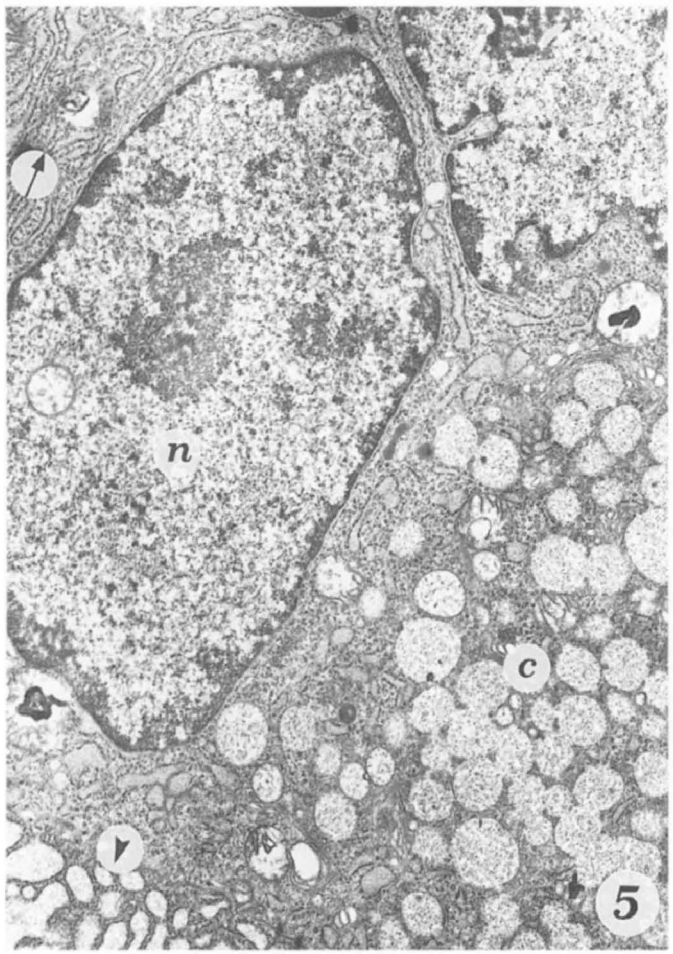
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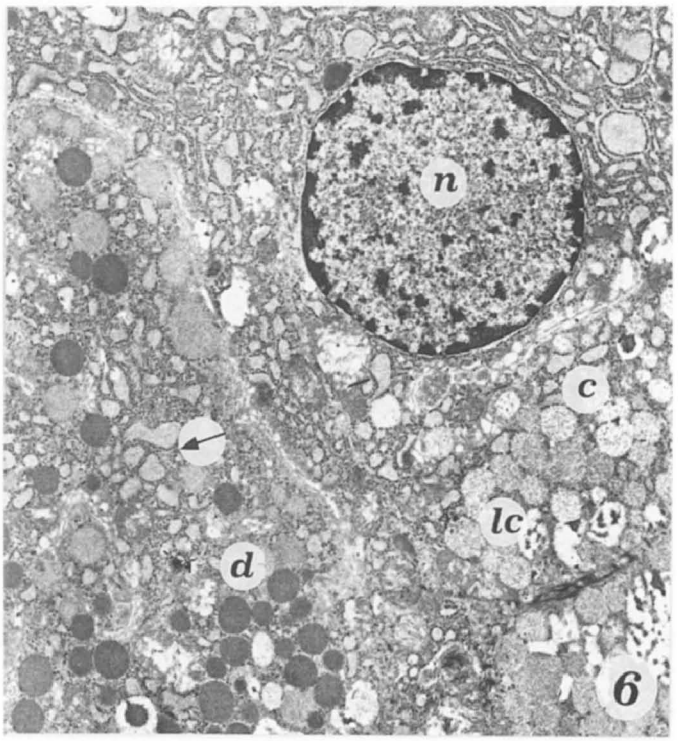
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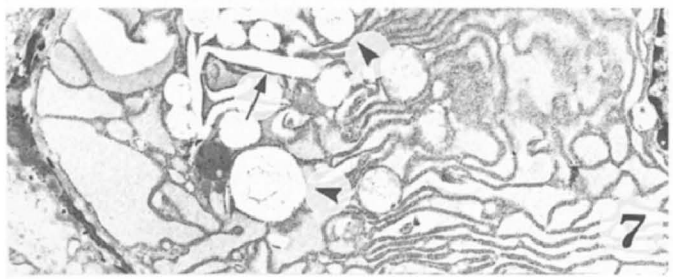
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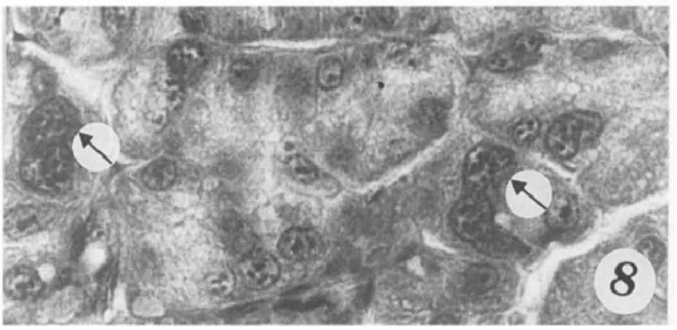
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side appeared as an ellipsoidal or pyriform, flattened disk often exhibiting a marked peduncle (Fig. 1), while the contralateral gland appeared roundish or slightly oval in shape and thicker (Fig. 2).

Our histological observations also revealed the different structural architecture of the two glands on opposite sides. In particular, the ellipsoidal gland was composed of three main lobes, drained by secondary excretory ducts that ran, in most cases, parallel to the gland surface and flowed into the main excretory duct, situated in the deeper portion of the gland and coming out of the peduncle. The roundish gland, on the contrary, presented only two main lobes: one of these was drained by ducts similarly arranged to the contralateral gland, whereas in the other lobe the ducts ran perpendicular to the gland surface and the main excretory duct came out of the dorsal part of the cranial margin of the gland.

The gland parenchyma was constantly found to be PAS-negative, while other features such as acinar cell size, acinar borders and connective content presented shape-dependent structural variations.

The acinar areas ranged between 1 500 and 3 500 μm^2 and the values of cell areas between 160–220 μm^2, but the variations between glands of opposite sides in rats of the same age did not prove to be statistically significant, even if higher in the ellipsoidal than in the roundish glands.

In particular, both glands in 70-day-old rats exhibited acini variable in size and clearly delimited by plentiful connective tissue. The cell borders of the ellipsoidal gland were easily detectable, and slightly dilated intercellular canaliculi were observed. The nuclei appeared not to be uniform in shape and size, with a diameter ranging between 3 and 6 μm, and were located in the basal part of the cell. The rough endoplasmic reticulum (RER) was well developed, consisting of dilated cisternae filled with rarefied material. Numerous granules with a clear or less clear non-homogeneous matrix were present; these coalesced to form vacuoles of varying sizes, sometimes as large as the nucleus, giving it a half-moon shape (Fig. 3).

In the contralateral roundish gland, the cell borders were less evident and the intercellular canaliculi were more numerous. The round or oval nuclei varied up to 10 μm in diameter, and others showed condensed chromatin and a wavy envelope. Acinar cells exhibited a variability, depending on their functional state. In particular, some of these, completely filled with parallel arrays of closely packed cisternae of RER, showed scattered little non-homogeneous granules in the apical cell portion. Some cells had a reduced RER with dilated cisternae and numerous non-homogeneous granules scattered throughout the cytoplasm, smaller than in the contralateral gland; others showed vacuoles of different size and markedly dilated RER with the intracisternal matrix less dense than the extracisternal one, with the result that the RER appeared to be sponge-like (Fig. 4).

In 80- and 90-day old rats, acini of the ellipsoidal gland were larger and more closely-packed, in the contralateral gland they were well delimited by connective tissue.

Ultrastructural examination revealed that the cells of the ellipsoidal gland in 80-day-old rats were variable in size and not clearly delimited, showing nuclei not uniform in shape and size (2–4 μm), some of them giant (10–15 μm). Several cells showed similar features to the ellipsoidal glands from 70-day-old rats as far as the non homogeneous granules and RER were concerned. Other cells presented parallel cisternae of RER, and occasional lipid-like structures were observed in the cytoplasm, with little lipid droplets (Figs. 5–7).

In the contralateral gland, the cells, the borders of which were more clearly visible, showed nuclei not uniform in shape, some of them containing condensed chromatin. Several giant nuclei were also present (Figs. 6–8). Among cells showing numerous clear and less clear non-homogeneous granules, there were a few cells containing dark granules. Vacuoles, abundant RER and lipid-like structures were observed in the cytoplasm (Fig. 7). Intercalated canaliculi were never clearly detectable in either gland.

In 90-day-old rats, the nuclei of the ellipsoidal gland were round or oval, the RER was abundant and in some cells appeared sponge-like, or contained closely-packed cisternae. Numerous cells were characterized by a large number of non-homogeneous granules, coalescing to form vacuoles (Fig. 8).

In the controlateral gland, the nuclear features appeared similar to those found in the roundish glands from 80-day-old rats (these features were already present in the histological sections). Several cells showed the RER to be sponge-like and others had large vacuoles, sometimes deforming the nucleus into a half-moon shape; dark granules were present together with abundant non-homogeneous granules. A few cells contained lipid droplets. Intercellular canaliculi seemed to be more noticeable than in the ellipsoidal gland (Fig. 9).

▶

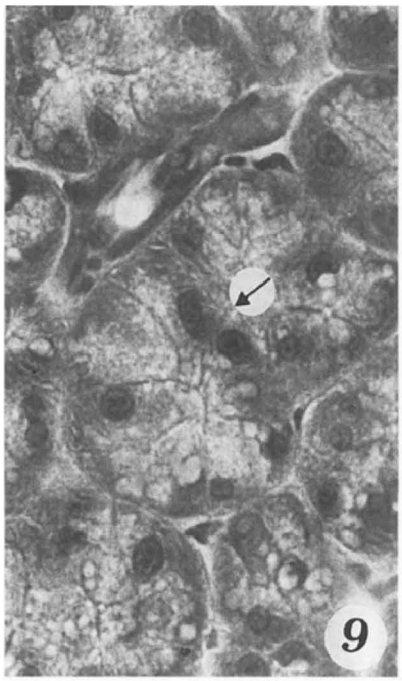
Fig. 9. Histological section of ellipsoidal gland of 90-day-old rat. In some acini the sponge-like RER (arrow) is evident. ×450

Fig. 10. Roundish gland cells of 90-day-old rat with clearly visible intercellular canaliculi (i). ×4 600

Fig. 11. Ellipsoidal gland cells of 120-day-old rat. Both sponge-like RER (arrows) and closely packed cisternae (arrow-head). Clear (c), less clear (lc) and dark granules (d), vacuole (v), intercellular canaliculi (i) and nucleus (n). ×5 300

Fig. 12. Ellipsoidal gland cell of 120-day-old rat. Evident severe cell vacuolization (v), intercellular canaliculi (i), nucleolus (n). ×5 300

Fig. 13. Histological section of ellipsoidal gland cell of 120-day-old rat. Some cells exhibit large vacuoles (arrows) while in others a cytoplasmic disorganization is evident (arrow-head). ×450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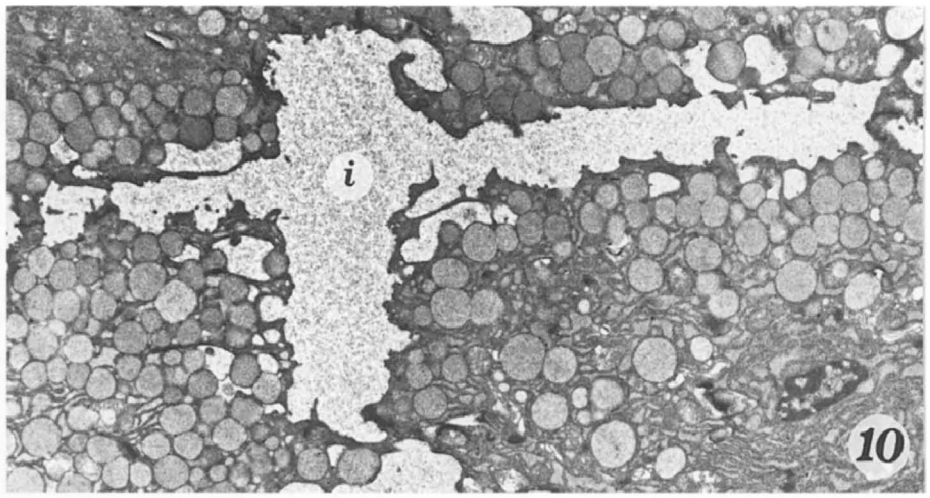
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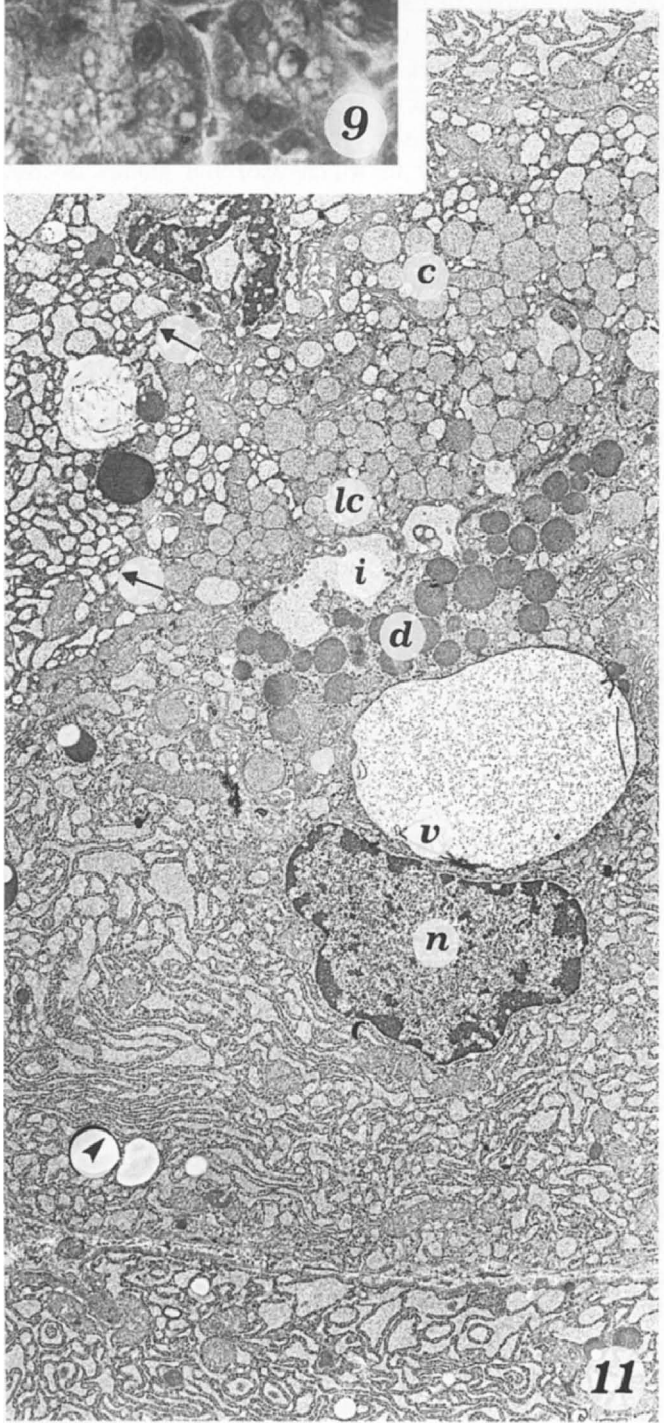
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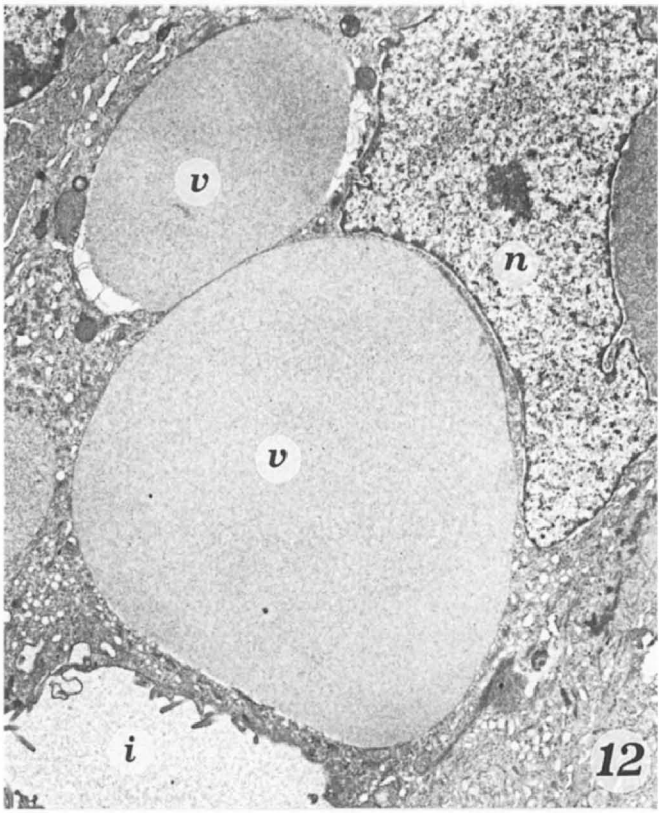
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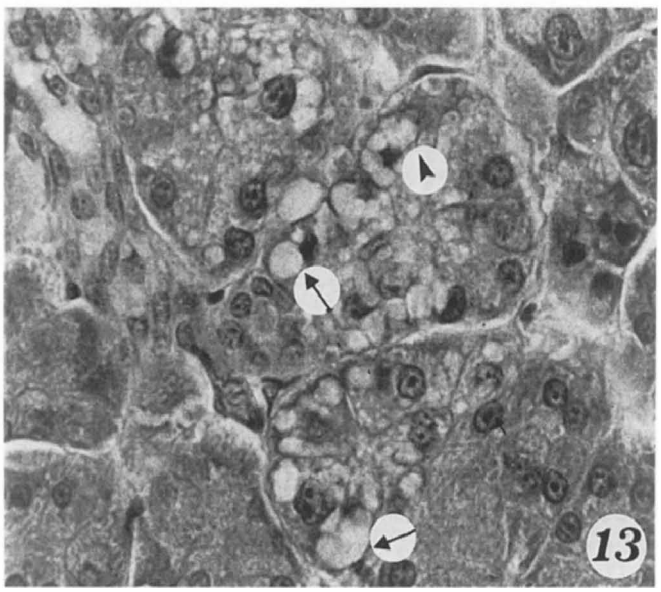
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In 100-day-old rats, the ellipsoidal gland presented quite large acini, clearly divided by connective tissue, whereas in the contralateral gland, they were smaller; the cell borders were quite detectable. In both glands the nuclei were variable in size and shape, some of them presented condensed chromatin in the roundish one, others were giant-shaped. In both glands the RER was abundant with slightly dilated cisternae, and little non-homogeneous, dark granules were observed. Finally, the ellipsoidal gland cells showed lipofuscin-like inclusions and were more vacuolized than the contralateral gland cells.

In 120-day-old rats, the ellipsoidal gland showed acini large in size, even if not so closely-packed as in the contralateral gland. The cell borders and nuclear features were similar to glands of same shape from 100-day-old rats. The majority of cells showed sponge-like RER; others well-organized RER. Non-homogeneous granules were widely scattered in the cytoplasm and coalesced to form large vacuoles (Fig. 11). In some cells a severe disorganization was observed, essentially due to the large size of vacuoles (Figs. 12–13).

The roundish gland cells showed oval nuclei with condensed chromatin. As far as RER organization and granules content were concerned, no noteworthy differences were detected in comparison with the ellipsoidal gland. Dark granules were present in both glands.

Discussion

The present study of male albino Wistar rats confirms and extends our previous macroscopic observations and histological data on the bilateral dimorphism of Loewenthal's gland in 180-day-old male albino Sprague-Dawley rats (Ricciardi et al. 1994, 1995). In particular, all the animals belonging to the same age group exhibited a side-specific ultrastructural dimorphism. The more marked structural variations in acinar size, cell size, shape and borders, nuclear size and shape, RER morphology and granular content, were more present often in glands in which a clearer macroscopic side-specific dimorphism was observed.

Ultrastructural examination also revealed a certain degree of individual variability, sometimes involving cells of the same acinus; however, it is likely that this heterogeneity might be due to different functional stages. Based on the ultrastructural features observed in the present study, we generally agree with Scott and Pease (1959), in particular concerning the presence of "light and dark" granules in young rats. In addition, we constantly observed that light granules could be further subdivided into clear and less clear non-homogeneous granules, with a marked tendency to coalesce and to form large vacuoles, whereas Scott and Pease affirmed that the light granules do not coalesce, maintaining their limiting membranes. In 1971, on the basis of his cytochemical analysis, Essner had already reported three types of secretory granules differing in "opacity"; he ascribed this difference either to differences in the degree of condensation or to different granular contents or to experimental artifacts. We also observed a similar three-graded opacity, despite the absence of any cytochemical process potentially interfering with the granular structures. We therefore suggest that the different granular opacity, involving clear and less clear non-homogeneous granules, is not due to experimental artifacts, and must stem either from structural differences or from a non-homogeneous condensation of the granule content.

In a previous study Ichikawa and Nakajima (1962) did not observe any dark granules in acinar cells of exorbital glands, but only light granules. This discrepancy could be ascribed to the scantiness of dark granules in the gland: our observations revealed that dark granules were much less numerous than light ones, and in particular, we never found any dark granules in glands from 70- and 120-day-old rats or in the ellipsoidal gland from 90-day-old rats. It is likely that Ichikawa and Nakajima analyzed a time-window in which exorbital glands do not express dark granules. As regards the acinar PAS-negativity, we agree with Ichikawa and Nakajima, bearing in mind that even among the authors (Scott and Pease 1959; Bignardi and Aureli 1962; Essner 1971; Sashima et al. 1989) who described the gland as sero-mucous on the basis of its PAS-positivity, Quintarelli and Dellovo (1965) and Spicer and Duvenci (1964) reported only a faint PAS-positivity in the mouse and the rat. Further analysis needs to be carried out to ascertain the chemical composition of secretory material located in the gland in order to clearly establish the cause of these discrepances.

As regards the RER ultrastructure, our observations agree with those of Luciano (1967), who described an irregular sponge-like arrangement of the RER, which she considered to be one of the typical adult male features; nevertheless, in several cases of male glands examined we did not find this feature. For instance, we detected this typical RER arrangement in the roundish glands of 70-day-old rats, but never in the contralateral glands. Therefore, sex differences should also be evaluated on the basis of the bilateral dimorphism.

It is well known that some paired organs can give a different response to hormonal influence, such as the female genital system of birds and, in mammals, the uterine horns of *Camelus dromedarius*, in which the left one is more developed (Zaganelli and Benvenuti 1975). Likewise, the ultrastructural bilateral dimorphism could be due to a different response of the glands of the two sides to the same hormonal factors as androgens (Cornell-Bell et al. 1985) and/or to some yet unknown pituitary or pituitary-dependent factors, as hypothesized by Azzarolo et al. 1995, which might be able to regulate certain gland functions. Moreover, in our previous study (Ricciardi et al. 1994), we noticed that the connective tissue content did not appear to correspond in the Loewenthal's glands of two opposite sides and neither did the respective vas-

cularization with its specific pattern. In keeping with that, it has been reported that differences in blood flow, via different routes, could induce seminal morpho-functional effects; this is the case of the adrenal chromaffin cells, which can produce either adrenaline or noradrenaline, depending on the blood supply (Wurtman and Pohorecky 1971).

In conclusion, our findings demonstrate that several contrasting data in the literature dealing with the structure of the Loewenthal's gland might be explained, at least in part, by the functional side-dependent dimorphism of the organ.

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Accepted March 25, 1999