THE HARDERIAN GLAND: ITS TUMORS AND ITS RELEVANCE TO HUMANS*

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INTRODUCTION

TO MOST PHYSICIANS AND VETERINARIANS, THE HARDERIAN GLAND IS BEST KNOWN from experimental work performed in rodents. The chemical induction of tumors in the harderian glands of mice increases the relevance of the question of whether a harderian gland exists in humans. This paper reviews the literature and the findings on examination of sections of adults and fetal adnexal and orbital tissues with regard to this question and concludes that there is not a harderian gland present in man.

The harderian gland was first described in two species of deer by Harder in 1694.[1] He originally called it "Glandula nova lachrymalis" because he realized that he had recognized a previously undescribed gland near the nictitans gland, the latter structure then known as the "Glandula lachrymalis." According to Miessner,[2] at the time the lacrimal gland was called the "Glandula innominata." During the 18th century any glandular tissue in the medial aspect of the orbit became referred to as the harderian gland, so that the distinction between the harderian gland and the nictitans gland was lost.

With histological studies of the gland begun in the late 19th century, the distinction between the two glands was again appreciated. Loewenthal in particular developed criteria which are used to distinguish the harderian gland.[3,4] The current accepted nomenclature for the harderian

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gland is the "Glandula palpebrae tertiae profunda" and the nictitans gland the "Glandula palpebrae tertiae superficialis." The nictitans gland is recognized as an accessory lacrimal gland aiding in the lubrication of the nictitating membrane. The functions of the harderian gland often vary with classes and orders, and even within the same species are often a matter of speculation and controversy. The present report reviews the status of our knowledge of the harderian gland and gives the evidence of the present authors for their conclusion that it is not found in man.

PHYLOGENY

Since the early anatomical and histological description of the harderian gland, numerous authors have described similar glands within the orbit and in the region of the nictitating membrane, or third eyelid, in a number of species, including amphibians, reptiles, birds, and many mammals.[5,6] The gland is quite large in frogs and reptiles, particularly in certain serpents called the thyphlopidae, in which it practically fills the orbit, being ten times larger than the rudimentary eye.[7] Birds also possess a very large harderian gland that secretes a thick, oily fluid. Among mammals it may also be large, especially in rodents. Prince et al[8] report the absence of the gland in dogs, cats, goats, and sheep, but does so making the personal, somewhat arbitrary distinction that any gland within the nictitating membrane is a nictitans gland and only an obviously separate gland can be called a harderian gland. They state, however, that in cattle the nictitans and harderian glands are surrounded by a common sheath, and they speculate that this may represent a stage in the evolutionary separation into two distinct glands such as are found in the pig or rabbit.

Two major theories that attempt to explain the embryological origin of the lacrimal and harderian glands are the "single gland" or "migration" theory and the "two glands" theory. The "single gland" or "migration" theory was first put forth by Wiedersheim[9] in 1908. It proposes that the lacrimal gland and the harderian gland share a common origin from a single gland situated in the lower lid. This theory proposes that a single lacrimal gland precursor is the source of all the accessory glands of the eye. Further, the growth of the nasal portion of this lacrimal gland precursor produces the sebum-secreting harderian gland, while the remaining portion moves temporally to the lateral canthus and then to the upper lid and becomes the lacrimal gland, which secretes tears. The theory assumes that the histologic architecture of the lacrimal and harderian glands is similar. Thus, the existence of two histologically distinct glands

in reptiles, birds, and mammals is not well explained by this theory. The alternative "two glands" theory proposes the existence of two histologically separate glands, the lacrimal gland in the outer canthus and the harderian gland in the inner canthus, and assumes that these arose from a common precursor gland during the course of vertebrate evolution.

Sakai[10] observes that the histologic structure of the harderian gland in one class of vertebrates has similarities to the lacrimal gland in the same class. He further notes that harderian glands from different classes are markedly distinct in their histological structures. In addition, mammalian harderian glands secrete lipid, whereas those of lower vertebrates secrete serous or mucous substances. Sakai concludes that phylogenetically the harderian glands of mammals may not be homologous to those of the lower vertebrates. Furthermore, the development of the harderian gland parallels that of the lacrimal gland, and the morphologic appearance of serous acini, characteristic of lacrimal gland tissue, within the excretory duct or the substance of the harderian gland itself is evidence of a possible phylogenetic association between the lacrimal and harderian glands. Thus, ancestral mammals may have developed the harderian gland from the lacrimal gland. The former now occurs commonly in many mammalian species, with possible secondary loss in some groups, most notably the primates.

ANATOMY AND HISTOLOGY

Sakai's definition of the harderian gland is most useful: "The mammalian harderian gland is (sic) those ocular glands that have tubuloalveolar endpieces (tubular alveoli) and secrete lipid by a merocrine mechanism."[10] Most glands are macroscopically identified on the basis of the location of the openings of their ducts on the inner surface of the third eyelid (although in rodents the duct opens on the outer surface of the third eyelid).

The gland is not always associated with a nictitating membrane, as in whales, in which there is no third eyelid at all but a harderian gland exists. Also, not all glands associated with a third eyelid are harderian glands; ie, the nictitans gland in the dog is remarkably different histologically from the "characteristic" structure of the harderian gland as observed in rodents.

Most of our knowledge of the harderian gland is derived from studies in rodents. The gland occupies the posterior portion of the orbit. The murine harderian gland appears to be speckled with dark brown pigments[11] due to the existence of porphyrin in the alveolar lumina.[12] The gland in

some rodents (gerbils) is also dark due to the presence of melanocytes in the interstitium.[13]

In the rabbit, the harderian gland is a large organ, approximately 19 mm long, 12 to 15 mm wide, and 4 to 6 mm thick, with two well-defined lobes. Both lobes are tubuloalveolar glands, with secretory portions of the gland emptying into ducts which open in turn into the inferior portion of the inner surface of the nictitating membrane. The stroma between the secretory portions stains positively with reticulin stains and periodic acid-Schiff, and has been described to contain significant amounts of fat cells and plasma cells.[10,14,15] The larger lobe, which appears pink in color, is composed of lipid-containing cuboidal epithelium with basally displaced nuclei and prominent nucleoli, surrounding central lumina (Fig 1). The smaller lobe, which appears white, has cuboidal and columnar epithelium, also with basally displaced nuclei, and narrower central lumina (Fig 2). The higher content of lipid droplets is probably responsible for the white color in this lobe.

The secreted material in the rabbit is sudanophilic, consisting primarily of neutral fats, phospholipid, alkaline phosphatase, and neutral glycopro-

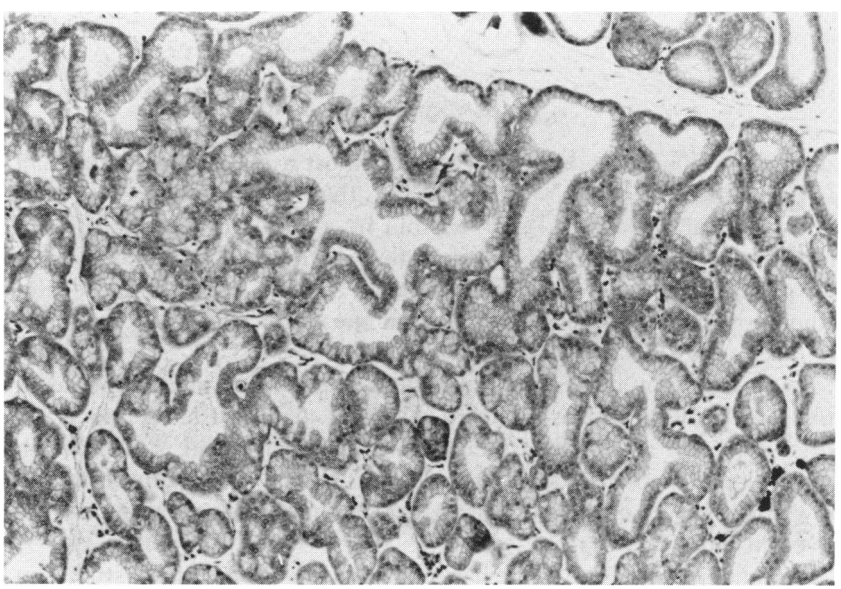

FIGURE 1
Pink lobe of harderian gland, showing low cuboidal epithelium with basally displaced nuclei. Note prominent vacuolization of epithelial cell cytoplasm (rabbit, hematoxylin and eosin, × 200).

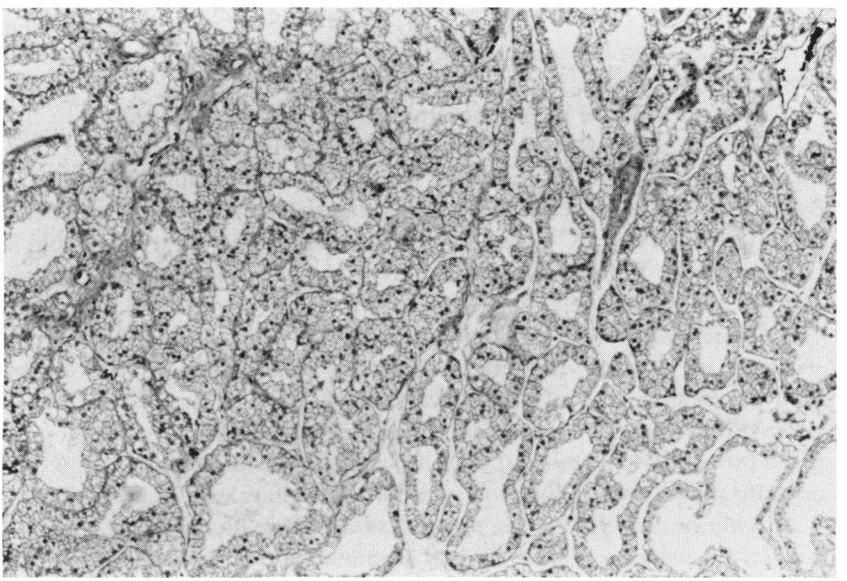

FIGURE 2
White lobe, showing cuboidal and columnar epithelium, also with basally located nuclei and occasional myoepithelial cells. Note plasma cells in interstitial areas (rabbit, hematoxylin and eosin, × 75).

teins. In addition, acid phosphatase is present in the white lobe, with small amounts of acetal lipid in the ducts and blood vessels, and sodium dioxidase is present in both lobes of the gland.[14] The alveoli of the harderian gland, in addition to secretory cells, contain myoepithelial cells, which are thought to aid in the expulsion of the acinar contents. The murine harderian gland is similar, showing a simple branched tubuloalveolar morphology with wide lumina, no duct system within the gland, no lobulation, and is primarily lipid-secreting.

In rodents, and other species as well, the harderian gland is histologically distinct from the lacrimal gland. The lacrimal gland shows acini with narrow lumina, a branched duct system within the gland, and prominent lobulation of the gland. Islets of serous acini have been found within the substance of the harderian gland in some species, which are considered to be ectopic lacrimal gland tissue.[10]

By electron microscopy, mice, rats, hamsters, and rabbits demonstrate two types of glandular cells, based primarily on the size and shape of their secretory vacuoles. "Light" and "dark" cells have been described in the secretory epithelium of the hamster harderian gland, based on their

overall electron density (Fig 3). "Dark" cells possessed more abundant ribosomes, larger and more numerous vacuoles, and more mitochondria than the "light" cells.[16]

Also on the basis of ultrastructural changes "A" and "B" type cells have been described. Dark concretions within alveolar lumina and the secretory vacuoles of type "B" glandular cells have been demonstrated in mice by the electron microscope, suggesting that these cells selectively secrete porphyrins.[17] Type "A" cells, on the other hand, may be responsible for lipid secretion. In most non-rodents, however, only one type of glandular cell has been described.

Electron microscopic findings confirm a merocrine or exocytotic type of secretory mechanism. Smooth endoplasmic reticulum is well developed, with the arrangement of tubules varying in different species. Numerous microvilli project from the apical surface membrane into the lumen of the gland tubules. Myoepithelial cells lie within their basal lamina, and demonstrate myofilaments that run parallel to the long axis of the cell.

Adrenergic and cholinergic terminals have been identified in hamster[18] and rat[19] harderian glands. Nerve terminals are in contact either with secretory or myoepithelial cells in rabbits and hamsters, or in association with the alveolar endpieces in rats and mice.[10] It appears that the parasympathetic fibers of harderian glands, similar to those of the lacrimal gland, course through the zygomatic nerve and are relayed via the pterygopalatine ganglion.

FUNCTION

The function of this gland has long been a matter of speculation. In lower animals, the harderian gland appears to be primarily involved in lubrication of the nictitating membrane.[14] Wolff[7] reports that in animals, a well-developed lacrimal gland is usually associated with a poorly developed harderian gland, and vice versa. Wendt,[23] notes that the harderian gland appears to be primarily sebaceous in lower and marine mammals, becoming more like a serous gland in higher mammals. Indeed, in cormorants and ducks, the harderian gland secretes a thick, oily fluid which is thought to protect the corneal surface from seawater. In crocodiles and snakes, the harderian gland provides accessory salivary secretions which aid in the lubrication of ingested prey.[5] A bacteriocidal effect has even been attributed to the glycerine ethers present in the secretions of the rabbit harderian gland.[24]

The mammalian harderian gland is classified into four types by Prince et al[8]: (1) lipid secreting, present in most mammals, some with very high

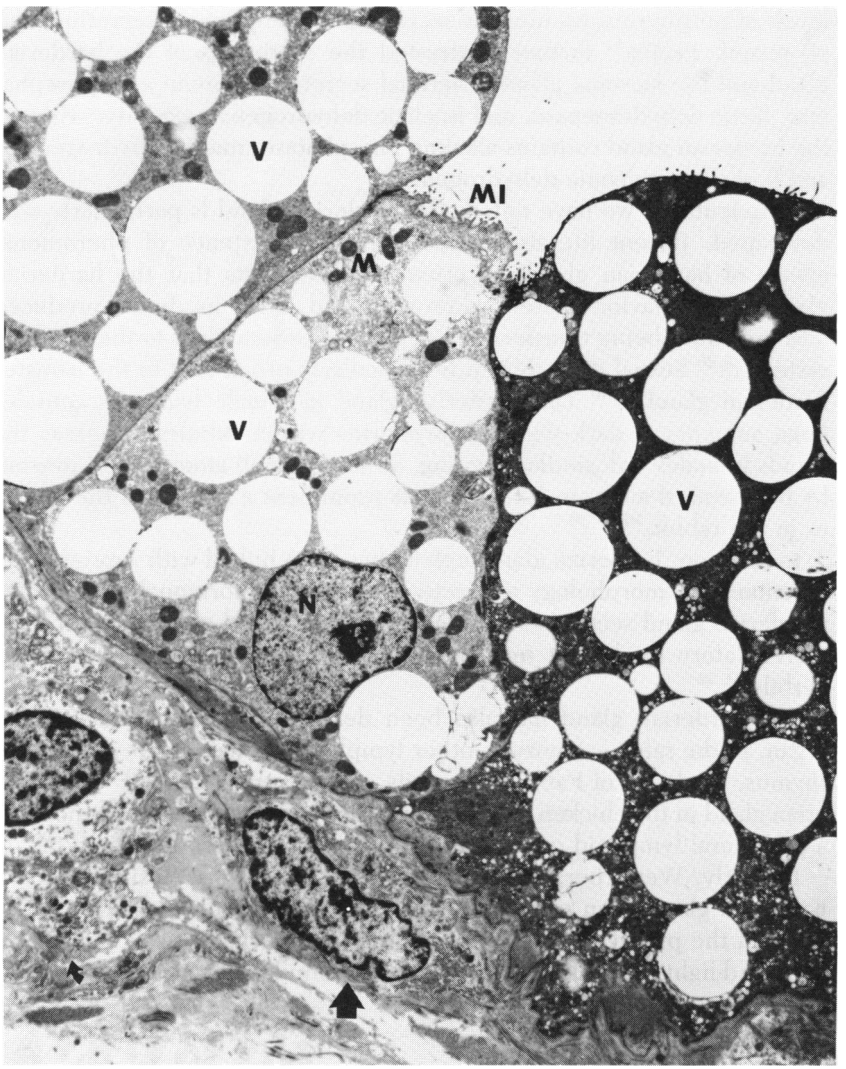

FIGURE 3
A general view of light and dark cells having columnal and cuboidal shapes. Note numerous large lipid vacuoles (V), mitochondria (M), microvilli (MI) projecting into lumen, and nuclei (N) located at basal portion of cells. Also cholinergic and/or adrenergic (*small arrow*) and myoepithelial (*large arrow*) cells are present (× 4160).

levels of porphyrins; (2) mucous secreting; (3) seromucoid secreting; and (4) mixed. Prince[14] further contrasted the secretions of the harderian gland and the lacrimal gland. Lacrimal secretions contain acid phosphatase, lactic dehydrogenase, and isocitric dehydrogenase activity, whereas the harderian gland contains alkaline phosphatase, malic dehydrogenase, and 6-phosphogluconic dehydrogenase.

In rodents, as we have noted, the harderian gland is particularly well developed. Recent literature documents the existence of pheromonal effects of harderian gland secretions, and suggests that the harderian gland is a behavior-related odiferous gland, with harderian-produced olfactory clues being transferred via the nasolacrimal duct to the olfactory system.[25,26] Sexual dimorphism is particularly prominent in the hamster harderian gland.[27-30] The harderian gland in female hamsters contains large amounts of dark-staining porphyrins within tubules, whereas the glands in males lack similar staining, although small amounts are present by biochemical analysis. This is not as prominent a finding in the mouse or in the rabbit.[16,28,30]

In addition, harderian gland activity has been linked with reproductive function with morphology and activity related to hormonal control.[25,26] Harderian gland secretions have also been proposed as a source of thermoregulatory lipids that may play a role in coat color maintenance in gerbils.[31,32]

The harderian gland has also been described as a lymphoepithelial organ, in the same category as other lymphoepithelial organs such as the thymus, the bursa of Fabricius, tonsils, and Peyer's patches.[15] The harderian gland in the chicken has also been used experimentally as a model of a peripheral lymphoid organ capable of immune response activity.[33-35]

Recently, Wetterberg et al[36] and Toolan[37] have hypothesized that the harderian gland is an extraretinal photoreceptor involved in the persistence of the pineal rhythm, possibly by such mechanisms as porphyrin-mediated light transduction, direct neural stimulation, or endocrine function.

PATHOLOGY

Involvement of the harderian glands of rats occurs in the condition known as sialodacryoadenitis, first described by Innes and Stanton in 1961.[38] This is an infectious disease complex whereby one or more of the salivary and lacrimal glands become inflammed with associated hypertrophy of the harderian gland. Keratoconjunctivitis sicca may result from decreased tear production in this disorder.[39] If the harderian gland alone is in-

volved, a nasal keratitis, frequently with anterior synechiae, may develop and persist as a permanent corneal scar. Microscopic lesions in harderian and lacrimal glands include necrosis of secretory and ductal epithelium with both acute and chronic inflammatory cell infiltrates, filling of ducts with inflammatory exudates, and squamous metaplasia of the ductal epithelium.[22,40] This disease is now recognized as being caused by sialodacryoadenitis virus (SDAV), a rat coronavirus.[41]

Figge et al[42] and Prince[14] have correlated an increased incidence of cancer in rats, hamsters, and mice with a higher porphyrin content of harderian glands. The accumulation of porphyrins within the gland is thought to be due to the lack of a metal-chelating enzyme.

Tucker[43] recently reviewed spontaneously occurring tumors in the harderian glands of mice, which have an incidence of 2.9% to 4.5%. These included the following epithelial tumors: adenomas (3.3%), cystadenomas (30.0%), papillary cystadenomas (46.7%), adenocarcinomas (16.7%), and undifferentiated carcinomas (3.3%). No lymphoid tumors were noted. Sheldon and co-workers[44] reported a larger series of mice, in which the overall incidence of spontaneous harderian gland gland tumors was 4.7%. Adenomas were found in 2.8% of the males and in 5.1% of the females. In addition, 0.1% of males and 0.3% of females developed adenocarcinomas, several of which appeared to have arisen from adenomas. No tumors spontaneously arose before 6 months of age. BALB/c mice were found to be especially susceptible, with over 80% of the total number of tumors. Typical examples of the spectra of mouse harderian gland tumors are shown (Figs 4 to 9). Such spontaneously arising tumors in harderian glands have also been reported in rats, hamsters, and rabbits.[45-47]

The harderian gland appears to be relatively sensitive to tumor formation. Pleomorphic tumors have been induced in mice by treatment with polyoma virus.[43] Harderian gland tumors in mice have been used as an animal model for experimental studies of induced carcinogenesis by exogenous agents. Phillips and co-workers[48] reported on experiments using the harderian glands of mice for the study of the radiobiology of heavy charged particles.

Goerttler and co-workers[49] developed an animal model of two-stage carcinogenesis in which they dermally applied carcinogens to NMRI mice treated prenatally with 7,12-dimethylbenz(a)anthracene. The authors found that the former compounds were promotors for the induction of tumors in the harderian gland at a particular period in prenatal development.

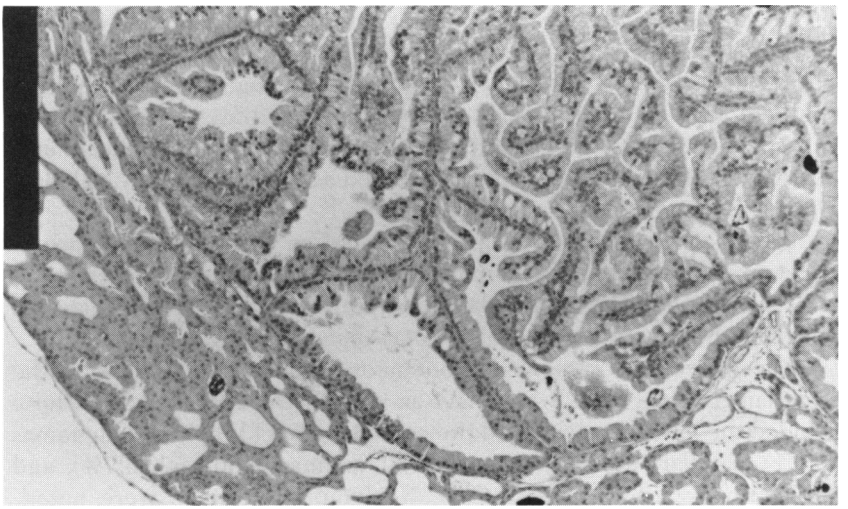

FIGURE 4
Typical pattern of growth of papillary cystadenoma. Tumor is clearly demarcated from surrounding normal gland and is composed of intraglandular papillary infoldings of neoplastic epithelium supported by a sparse stroma (mouse, hematoxylin and eosin, × 40).

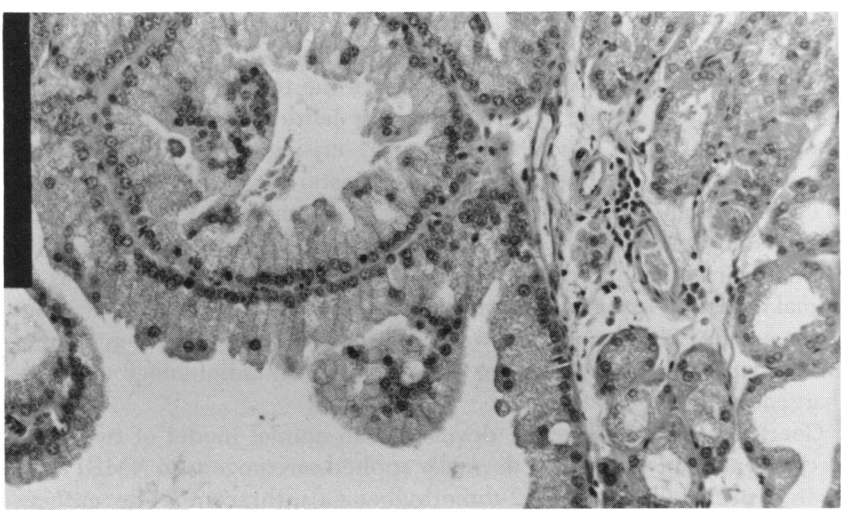

FIGURE 5
Morphologic features of epithelium typically found in moue harderian gland papillary adenoma. Compared to surrounding normal glandular epithelium height of neoplastic epithelium is greater. Cytoplasm of neoplastic epithelial cell contains numerous small vacuoles. Nuclei resemble those of normal glandular epithelium and are usually found basally. However, nuclei may be aberrently located and may be found occasionally clustered near gland lumen (mouse, hematoxylin and eosin, × 160).

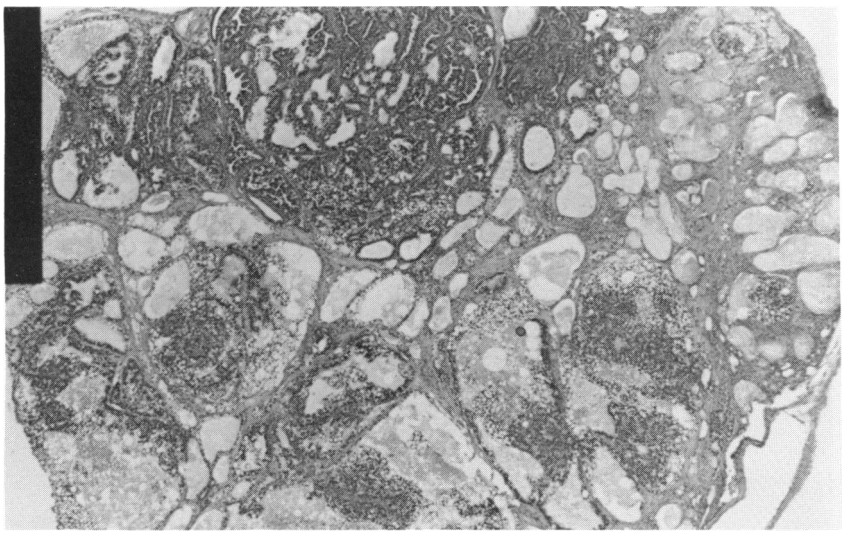

FIGURE 6
Demonstration of transitional stage of neoplasia from a cystadenoma to an adenocarcinoma. A nodular focus of densely packed epithelium is present as several foci of adenosis (mouse, hematoxylin and eosin, × 40).

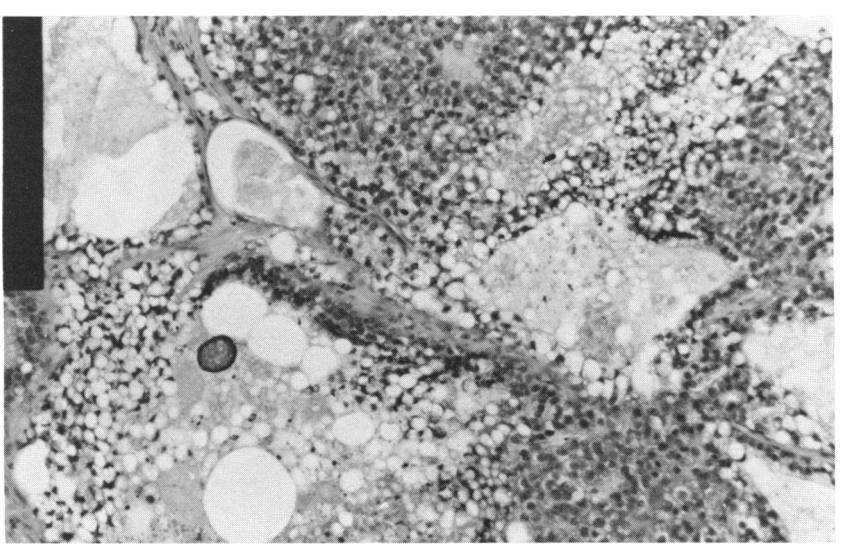

FIGURE 7
Characteristic feature of adenosis in mouse harderian gland adenocarcinoma is shown. There is little evidence of glandular formation and instead, there are sheets of epithelium. Frequently, cytoplasm of neoplastic cells in these foci is distended with prominent vacuoles. Nuclei are hyperchromatic (mouse, hematoxylin and eosin, × 125).

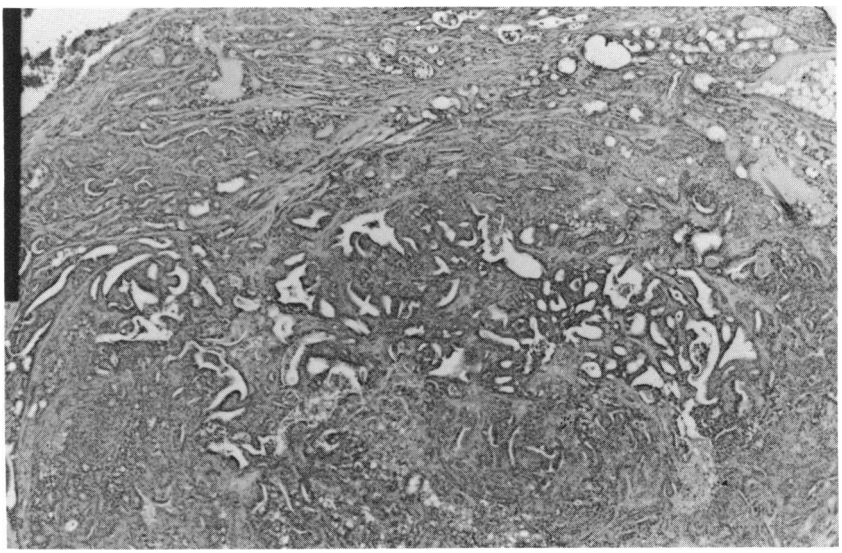

FIGURE 8
Adenocarcinoma composed of densely packed cells showing abortive attempt at glandular formation. There is no normal tissue present (mouse, hematoxylin and eosin, × 40).

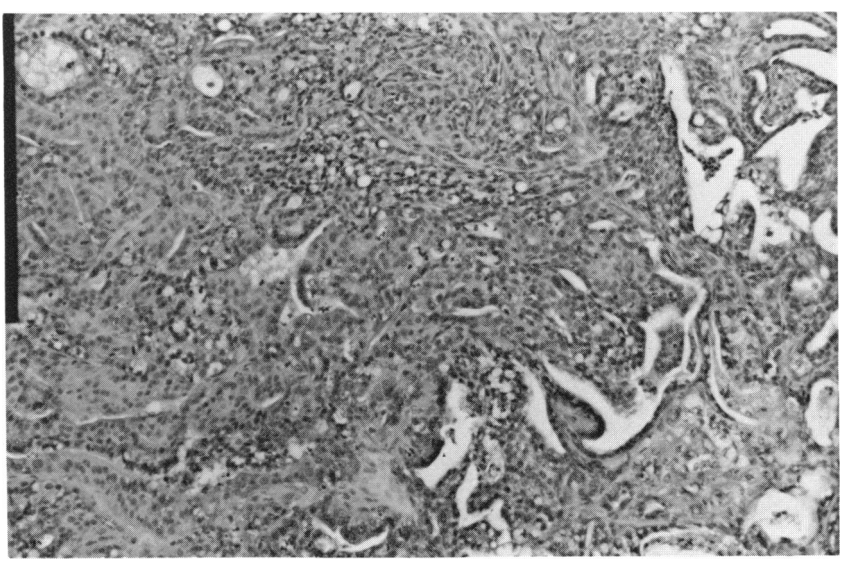

FIGURE 9
Adenocarcinoma demonstrating pseudoglandular formation by densely packed epithelium. Even at this magnification, pleomorphism of nuclei can be appreciated (mouse, hematoxylin and eosin, × 125).

RECENT IMMUNOLOGIC STUDIES

A recent development in the study of the harderian gland relates to the possibility that an antigen similar to guinea pig harderian gland antigen may be relevant in the pathogenesis of Graves' ophthalmopathy. Guiniea pig harderian gland membrane preparations have been documented to bind thyrotropin (TSH) and to have receptors for it. Andrews and Dunn[50] have looked at the effects of TSH on inducing certain biochemical changes in harderian glands, such as increased hexosamine content and increased uptake of ^{35}S into the chondroitin sulfate fraction of the gland. Additional authors[51-53] report the binding of immunoglobulin in the serum of patients with Graves' ophthalmopathy to guinea pig harderian gland antigens. This suggests that retro-orbital antigens in such patients are cross-reactive with guinea pig harderian gland, and may play a role in human Graves' disease and exophthalmos. The retro-orbital antigen may then be the TSH receptor. However, Kendall-Taylor and co-workers[53] identified antibodies to guinea pig harderian gland preparations in serum from patients with active Graves' ophthalmopathy, totally distinct from any potential binding activity to thyroid antigens. Furthermore, Bolonkin and co-workers[52] report that gamma globulins from patients with Graves' disease and exophthalmos were reactive, while globulins from patients without the exophthalmos were not.

In addition, human lacrimal gland antigens have also been implicated in ophthalmic Graves' disease. Wall and co-workers[54] have noted a clinical correlation between ophthalmic Graves' disease and enlargement and decreased function of lacrimal glands, and also between thyroiditis and Sjögren's syndrome. They demonstrated the transformation of peripheral blood lymphocytes in response to human lacrimal gland antigen in patients with Graves' ophthalmopathy. Stewart and Snell[55] link lacrimal, salivary, and harderian glands antigenically in describing spontaneously arising chronic atrophy of the three glands in rats with thymoma.

The experimental work described above raises the question of the presence of a retro-orbital antigen in humans that may be relevant to the pathogenesis of Graves' ophthalmopathy. Guinea pig harderian gland may contain an antigen which is immunologically identical to, similar to, or cross-reactive with a human retro-orbital antigen. Clearly, this retro-orbital antigen is distinct from both thyroid antigens and skeletal muscle antigens.[53] We suspect however that guinea pig harderian gland antigen employed by most investigators may not be truly specific for harderian gland, but rather may be found in other organs such as the lacrimal gland, salivary gland, mammary gland, or other lymphoepithelial glands.

A HARDERIAN GLAND IN HUMANS?

The presence or absence of the harderian gland in man has been a subject of controversy within the medical literature. Duke-Elder[5,6] states that "the gland is vestigial in primates and man." His basis for this statement appears to be Giacomini's[20] report of 1887 describing the gland in a human and Loewenthal's[21] 1910 study describing a transitory fetal structure in the inferolateral fornix. The latter contention appears unsubstantiated. Giacomini's study in contrast is intriguing, and deserves attention. The present authors were unable to obtain this report from any of the major medical libraries in the United States and the only copy finally located was in the British Library. Because of its rarity we include the following translation of the pertinent section.

Excerpt from "Notes about the Anatomy of the Black Race" by Professor C. Giacomini:

> Concerning the existence of Harder's gland in a Bushman—occurrence in the cartilage of the plica semiluminaris.
>
> Last February I had the opportunity of studying another black man. He is the fourteenth in my study. He came from central Africa close to N'Gami Lake . . . I had the chance to observe an extremely interesting peculiarity which has not been previously described in our species. Adjacent to the base of the cartilage of the plica semiluminaris there is a large glandular structure consisting of three lobules. The lobules are separated from each other by connective tissue. This gland has a close relationship with the cartilage, from which it is separated by adipose tissue.
>
> The division among the lobules is more evident on the lower part of the gland, while superiorly the lobules seem to be fused. Here you can find the excretory duct. It originates from the very center of the gland by the junction of the excretory duct of each of the three lobules. In deeper sections which are almost through the cartilage when the (above) glands are very small, I could see two additional little glands, one before the other. These latter glands are independent from each other and from the larger Harder's gland. They have their own excretory duct which opens, as does the excretory duct of Harder's gland, on the internal part of the plica semiluminaris. The glandular acini are divided by connective tissue in which are found occasional lymphocytes. The cells of the acini are conical with their base on the basal lamina and the apex of the lumen. There is only a single layer of cells. The nucleus has a basal position. The excretory ducts are characterized by a cylindrical epithelium in two layers.

> There is no doubt about the identity of the gland I described. This is what we call in animals Harder's gland or the gland of the plica semiluminaris. Since I found cartilage in the plica in members of the black race, I have previously searched for Harder's gland too, but my studies were unsuccessful. In fact presently the existence of this gland in humans is not admitted. However it is very often possible to find in the plica semiluminaris the small glands which are similar to the other small glands found in the conjunctiva. Some anatomists relate these small glands to Harder's gland in humans. The fact that in this man we found both these small glands and a true Harder's gland demonstrates that this is not true. The gland described is reminiscent to me of those described in two species of monkeys. (Ceropticeco; Cinofelo)

The work also includes drawings of the gland, which we believe closely resembles harderian gland (Fig 10). We interpret Giacomini's case to represent a unique atavistic choristoma. No other similar report could be found. Numerous articles denying the existence of a harderian gland in humans are available.[10,14,22]

We studied ten exenteration cases from the cases on file in the Eye Pathology Laboratory of the Massachusetts Eye and Ear Infirmary for the presence of harderian gland. The patients ranged in age from 17 to 74, and all had a diagnosis of malignant melanoma. Careful examination of these cases did not reveal any glandular tissue that was consistent with a harderian gland, although lacrimal gland tissue was easily identified. Therefore, from these studies we are unable to support the contention that a harderian gland exists in humans.

A further search of the files in Ophthalmic Pathology at the Institute of Ophthalmology in London yielded material from ten fetal orbits. The material was obtained from six individual patients. All of the orbits had been sectioned horizontally but only one or two sections were available for study from each. We found primitive lacrimal gland tissue in three of the specimens (Fig 11). We were unable to identify anything that resembled harderian gland in any of them.

CONCLUSION

Despite references in the literature suggesting a vestigial or transiently present harderian gland in humans, the only convincing report we could find was an apparent atavistic choristoma reported by Giacomini.[20] We find no histologic evidence to confirm the presence of a true harderian gland in humans, either in fetus eyes or exenteration specimens from

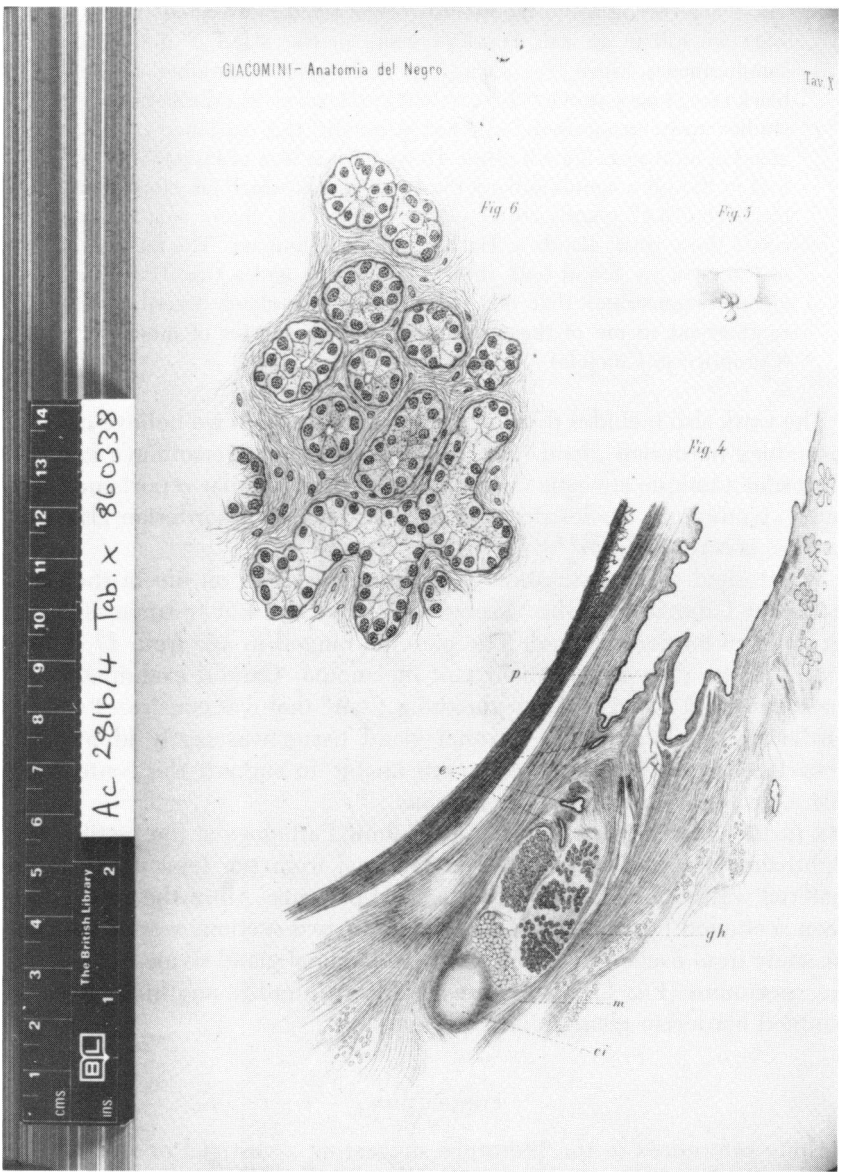

FIGURE 10
Reproduction of drawing by Giacomini showing histologic features of choristoma.

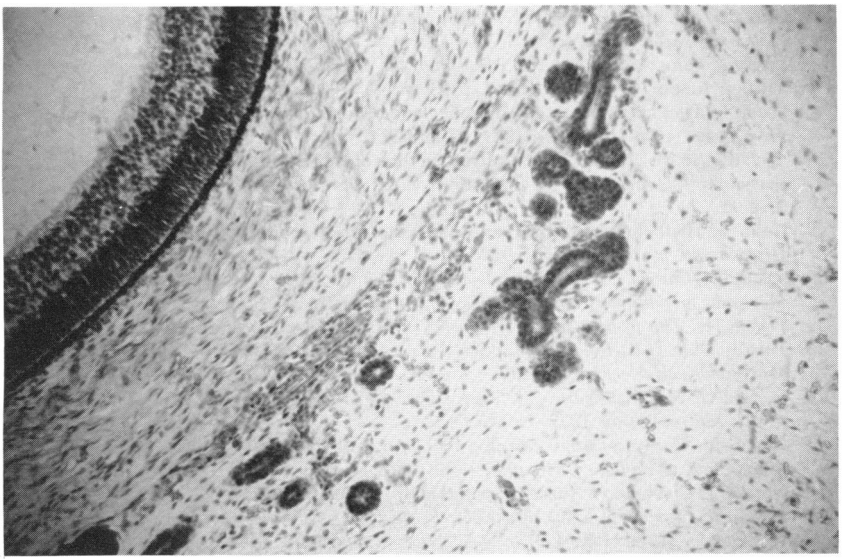

FIGURE 11
Human fetal gland found in review of sections of fetal orbits.

adults. The recent work concerning the guinea pig harderian gland antigen and human retro-orbital antigen raises the question of the existence of human harderian gland antigen in the absence of a true harderian gland. Most likely, guinea pig harderian gland antigen is cross-reactive with a human, non-harderian, retro-orbital or intra-orbital antigen, possibly lacrimal gland antigen. In summary we can find no evidence for the presence of a harderian gland in man.

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DISCUSSION

DR J. REIMER WOLTER. In its historical, anatomical, physiological, and pathological message, this paper is perfect and it is my duty as a discussor to emphasize its value. This study will end the somewhat obscure and mysterious position of Harder's gland in all our morphological and evolutional considerations. Doctors Frayer and Albert have exposed all the facts about this gland—and I have nothing to add on the level of their presentation.

What I can do, however, is to add some practical thoughts and questions to the authors with the aim to expose all the clinical potentials of the substance of this work: it is my impression that the secretions of the harderian gland serve to lubricate the nictitating membrane in an attempt of nature to obtain—and maintain—the most perfect corneal surface in animals that need extremely good visual acuity for their survival—birds, for example. These secretions are said to be distinctly oily and are sometimes known as "cetacea" in the old literature. Could biophysical and biochemical study of these secretions in animals allow for a new approach and a better understanding in the field of optimal corneal lubication to be used for artificial tears and for contact lens fluids in man?

But even more exiting thoughts along the same line are possible: the German book on *Human Physiology* by Landois that I used as a medical student in its 1943 edition mentions the nictitating membrane and the presence of Harder's gland in crocodiles and birds. And Landois goes on to state: "the tears of the snakes remain under the watch glass-like skin-covering that is continuous over the eye." And the present authors mention that the secretions of Harder's glands in snakes drain into the mouth and may have a part in digestion . . . When I read all this during my preparation for this discussion, I tried to get more information about the situation in snake eyes and I also tried to find a snake for my own histological study of its eye. But I failed in both instances. Our zoologists don't know much about snake eyes—and the snakes themselves still were in hibernation, when I looked earlier this spring.

If Landois should be correct in his statement about an optically clear skin with tear-like fluid under it covering the eye of snakes, we would have nature's own model for a living contact lens. This would be somewhat like epikeratophakia without direct corneal attachment. In our experimental attempts to recreate such a living contact lens for the correction of aphakia, for example, we could try to use the cornea of big fish. Successful corneal replacement in man with fish cornea has been mentioned earlier at this meeting by Doctor Kennedy. For a start this experimental procedure could be called "snake vision"—perhaps in its Russian translation to hide the origin of the idea and avoid unnecessary concern among our friends and patients.

In the process of getting my feet back on the ground, I would like to urge the authors to give us all their own thoughts about the practical values of their observations. May I thank the authors and the Society for allowing me to discuss this valuable paper.

DR DAVID G. COGAN. As many of you know I have had the great privilege of being closely associated with Doctor Kuwabara for many years. The harderian gland is one of his many recent interests. He has shown that in some rodents—I believe the rat—the gland wraps itself about the optic nerve and much of its secretion is into the nose rather than onto the conjunctiva. In view of this and of the gland's bisexual dimorphism—porphyrin is present only in the male rat—it seemed to us that the harderian gland might function to establish a territorial prerogative rather than to have any strictly ocular function.

DR W. JACKSON ILIFF. I very much appreciated and enjoyed Doctor Albert's paper. My comments are a little bit directed at some of Doctor Wolter's comments. In the snake, the lids are fused forming a "spectacle" covering the eye. The space between this "spectacle" and the cornea is filled with secretions of the harderian gland and lacrimal glands. There is a duct that then communicates to the roof of the mouth adjacent to olfactory organs in the snake where the snake will stick his tongue. These secretions contribute to the lubrication of prey. There is a report in the literature of a blockage of that duct in a Gaboon viper which produced marked dilation of this space giving a buphthalmic appearance. I have also seen a similar case in an albino block rat snake. We have this specimen in Doctor Green's laboratory and we have done serial sections or near serial sections through the globe but have not been able to demonstrate the communication to the roof of the mouth. Both of these snakes had the condition at birth. I do have the head of a normal black snake sitting on my desk which I am planning on looking at one of these days. Maybe Doctor Wolter would be interested in that.

DR DANIEL ALBERT. Once again, our society has demonstrated its unusual breadth of interest and I again thank the program committee for permitting us to present this paper. Doctor Frayer and I thank Doctor Wolter for his scholarly discussion. I think that there is value in learning more about the secretions of this gland which is so effective in protecting the cornea in other species. With regard to the vision of the snake, I can add nothing. I thank Doctor Cogan for his interesting comments and look forward to knowing more about Doctor Kuwabara's work, and also appreciate Doctor Iliff's remarks.