In ophthalmia produced in rats by diets deficient in vitamine A, lacrimation is an early symptom, whereas later the secretion decreases with a drying of the conjunctiva. This phenomenon suggested the possibility of an involvement of the paraocular glands in this condition. A second observation that led to investigation of the glands was the fact that the lesions resulting from dietary deficiency generally begin simultaneously in both eyes, with relatively little difference in the rapidity of development on the two sides. Although clinically one eye may appear to be unaffected, microscopic investigation shows that unilateral involvement is exceptional. These considerations indicate that while the character of the eye lesion is essentially that of a bacterial infection of the conjunctiva, there is probably some disturbance outside the eye which makes the infection possible. Since it is known that the lacrimal secretion has bactericidal properties, it seems possible that such a disturbance might lie in the activity of the glands that supply the secretion. A careful histological study of the paraocular glands, therefore, appeared warranted. Before presenting the findings, a brief discussion of the anatomy and physiology of these little studied glands may make for clearness.

In the majority of mammals, the conjunctival secretion is supplied by two small organs, the lacrimal and the Harderian glands. There

* This investigation was made in cooperation with Dr. Thomas B. Osborne and Dr. Lafayette B. Mendel, under whose direction the feeding of the experimental animals was conducted.
are, however, in addition, the Meibomian glands, specialized sebaceous glands which lubricate the margins of the lid, and numerous solitary mucous glands scattered through the conjunctiva of the lids.

In certain species, including the rat and mouse, the lacrimal apparatus consists of two parts, one, intraorbital, the other, extraorbital. The former lies generally behind the eyeball, while the latter is found near the angle of the jaw in close relation with the parotid.

### Table I.

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Body. gm.</th>
<th>Lacrimal and Harderian glands. mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.5</td>
<td>48.0</td>
</tr>
<tr>
<td>2</td>
<td>72.8</td>
<td>118.0</td>
</tr>
<tr>
<td>3</td>
<td>80.6</td>
<td>146.0</td>
</tr>
<tr>
<td>4</td>
<td>102.0</td>
<td>166.0</td>
</tr>
<tr>
<td>5</td>
<td>120.0</td>
<td>170.0</td>
</tr>
<tr>
<td>6</td>
<td>150.0</td>
<td>260.0</td>
</tr>
<tr>
<td>7</td>
<td>194.0</td>
<td>285.0</td>
</tr>
<tr>
<td>8</td>
<td>200.0</td>
<td>257.0</td>
</tr>
<tr>
<td>9</td>
<td>205.0</td>
<td>280.0</td>
</tr>
<tr>
<td>10</td>
<td>208.0</td>
<td>283.0</td>
</tr>
</tbody>
</table>

The Harderian gland is situated intraorbitally, generally in close apposition to the eyeball. In man, and other primates, it is a small vestigeal structure. In the rat, mouse, and rabbit, and other animals having a well developed nictitating membrane, or third lid, the gland is quite prominent, and in most of these species is considerably larger than the intraorbital lacrimal, with which, in the rat and mouse, it is closely associated. The relatively large size of the two glands is well indicated in Table I, which shows the weight of the body and of the two glands in ten normal rats.

The amount of gland tissue is proportionately far greater than in man, as the following comparison will show. The lacrimal gland in man, according to Canavan,\(^1\) who has recently made a study of the organ in forty cases of mental disease, has an average measurement

of not more than 2 by 1 by 0.5 cm. This would indicate a weight for the two glands of about 2 gm., or an approximate proportion of gland to body weight of about 1:25,000; whereas in the rat the average proportion, as the figures given in Table I show, is around 1:700, not including the extraorbital lacrimal. In other words, in the rat there is at least thirty times as much glandular tissue supplying secretion for the conjunctive as in the human being.

Owing to the close association of the Harderian and lacrimal glands, and the larger size of the former, we confused the two structures in our earlier studies. A review of the literature shows that this mistake has been made before. In Jordan and Ferguson's Text-book of histology, for example, there is a photomicrograph of "the lacrimal gland of the rabbit" which is evidently the Harderian gland. In the rabbit, it may be explained, the two glands are separate and can be easily distinguished grossly, as well as microscopically.

While both glands are acinotubular in type and are similarly lobulated, their component cells are different (Fig. 1). The lacrimal gland is made up of small acini which, at least in fixed preparations, appear to have little or no lumen. The marked shrinkage is, no doubt, the result of the watery character of the cells. The nuclei vary markedly in size and are rich in chromatin. The cytoplasm takes a definitely basophilic stain, like that of pancreatic epithelium. Large vacuoles are numerous.

In the Harderian gland the acini are larger and the cells are uniform in size with relatively small nuclei and abundant eosin-staining cytoplasm. In frozen sections, stained by Sudan III, or Sharlach R, the cytoplasm is seen to be filled with numerous fat granules of varying size. In paraffin preparations, granules obviously of a protein nature, and vacuoles left by the dissolved fat, are numerous. The form of the cells and acini is well shown in Fig. 2.

The exact nature of the secretion of the Harderian gland has not been definitely determined. According to Weber, its function is not essentially different from that of the lacrimal glands, although its

3 Weber, M., Die Säugetiere; Einführung in die Anatomie und Systematik der rezenten und fossilen Mammalia, Jena, 1904, 140.
secretion is more fatty in character, which is consistent with the fact that this gland is found especially in water mammals as a protection against the water medium, and is lacking in Chiroptera and Simiidae. Jordan and Ferguson, however, refer to the gland as a mucus-secreting organ. After Zenker fixation, we have observed in the lumina of the acini and ducts a variable quantity of yellow granular precipitate. This is not seen in formaldehyde-fixed tissue. This observation suggests that while fat may be present in the secretion, there are, undoubtedly, other elements of importance.

The paraocular glands were studied microscopically in 42 rats, including 15 with early ophthalmia, 15 with advanced ophthalmia, and 12 controls. The ophthalmia was produced, as described in the preceding paper, by a diet deficient in vitamine A. The rats were carefully observed and were killed at different stages of development of eye lesions.

The controls consisted of six healthy young rats of the same age as the experimental animals, and six old rats suffering from chronic skin and eye infections. The ocular tissues were fixed and sectioned, as previously described, except that in some instances the lacrimal and Harderian glands were dissected free from the eye and sectioned separately. A small part of the Harderian gland, however, was practically always left attached to the eye, to which it is closely bound.

The findings in the Meibomian, lacrimal, and Harderian glands can be best considered separately.

*Meibomian Gland.*

In a previous communication, describing the conjunctival lesions, we referred to the strikingly large Meibomian ducts, and Mori has reported a similar observation, regarding the change as a cystic dilatation. Since, however, ducts of comparable size have been seen in preparations from control animals, we are not certain that the change is pathological. It is known that the smaller Meibomian ducts unite to form larger ones, and it is probable that the very large channels seen in some sections are collecting ducts. No changes in the glandular epithelium have been demonstrated.

Lacrimal Gland.

Only the intraorbital lacrimal has been studied. On account of its small size, it was frequently overlooked in routine sections. It was this fact, as stated above, that led us in the beginning to confuse the lacrimal with the more conspicuous Harderian gland. According to Mori, the lacrimal gland in rats kept on a diet deficient in vitamine A shows a marked shrinkage of the secretory cells of the acini.!!

"They (the cells) no longer show secretory zones. The nuclei take on irregular shapes, occupy the central part of the cytoplasm, which is very small and stains very poorly. The individual acini of the gland become so small that it is impossible to distinguish them with the low power of the microscope, and the gland appears to be a simple mass of nuclei."

Mori also observed in the cells of some of the glands studied large vacuoles which, as specific stains showed, were spaces that had been occupied by fat droplets. The present study confirmed Mori's findings, but the significance of the observations should be questioned in view of the fact that similar histological pictures can be demonstrated in the glands of normal rats. Fig. 1, for example, shows in a gland taken from a normal animal changes which Mori has described. While there is clinical evidence of an altered secretion of the lacrimal gland, particularly in the later stage of dietary ophthalmia due to vitamine A deficiency, the histological changes described do not explain the phenomena, for the reason just stated. It is possible that special granule stains may be necessary to demonstrate the change. We have not observed, in the lacrimal gland, definite acute or chronic inflammation, such as is commonly seen in the Harderian gland.

Harderian Gland.

Lesions of the Harderian gland were found associated with both early and advanced ophthalmia, but the incidence of involvement was highest in rats showing advanced conjunctival changes. In only one instance were marked lesions seen in a healthy control. On the other hand, in one of the diseased controls, an old animal with skin and eye infection, the gland showed striking lesions.
Degenerative Changes.—The Harderian gland has been so little studied by pathologists that the normal variation in the form and staining properties of the acinar epithelium is not known. In some of the control specimens, a definite granulation and vacuolation of the cytoplasm were observed, while in many of the experimental animals, particularly those showing advanced ophthalmia, extreme vacuolation and an apparent disintegration of the cytoplasm were noted. This change is well shown in Fig. 3. In one gland, widespread necrosis of the epithelium was seen with only a slight, apparently beginning, inflammatory reaction, a lesion comparable to the necrosis of the renal epithelium in mercury or uranium nitrate poisoning (Fig. 4).

In general, we believe that the data are insufficient as yet to warrant a statement as to just what constitutes a degenerative change. It is possible that swelling, granulation, and vacuolation may represent variations in functional activity. A marked dilatation of the acini constitutes the most striking alteration in several preparations. In some, the change was diffuse (Fig. 5), but more often only a single lobule was affected.

Acute Inflammatory Changes.—In five of the glands studied an acute inflammatory reaction was found. The histological features of the reaction did not differ essentially from those seen in other glandular organs. Polymorphonuclear leucocytes were abundant, often filling the acini and widely infiltrating the interacinar tissue. In some instances, the lesions were focal, involving only one or a small group of lobules, but in many cases the entire gland was involved. In the majority the lesion was bilateral. The involvement of the ducts was a conspicuous feature in practically all specimens. In some the ducts were markedly dilated, and the lumen was filled with polymorphonuclear leucocytes and cellular debris (Fig. 6.) Abscess formation was the exception, rather than the rule, being seen in only two instances.

Chronic Inflammatory Changes.—The transition from acute to chronic lesions was not sharp, and as in other organs, there was frequently seen what might be termed a combination of acute and chronic inflammation; that is, the process was quite active, with numerous polymorphonuclear leucocytes, but associated with this
was evidence of healing, with granulation tissue and well developed scar tissue, and numerous phagocytic mononuclear cells. In two instances, the lesions were practically healed, leaving a scarred, atrophic gland. Figs. 7 and 8 show the varied picture which may result from the chronic inflammatory process. There is quite as much variation in the pathology of the gland as can be demonstrated in regularly studied organs, like the pancreas or thyroid.

**Lymphoid Cell Accumulations.**—In five rats, two of which were normal, discrete foci of lymphoid cells were found scattered through the glands. These nodules varied in size from a collection of a dozen cells to patches occupying a space equal to that of a group of acini. In one gland, three nodules were found that corresponded in every particular with those described by Canavan1 in the human lacrimal gland. The accumulations probably have no significance, and are to be classed with accumulations in the wall of the bronchi, kidney cortex, and other situations. In the present work, they were certainly not definitely related to the eye infection.

**SUMMARY.**

There is evidence suggesting that the ophthalmia which results from a deficiency of vitamine A is secondary to some change outside the eyes, and that this change may lie in the paraocular glands. In rats these glands consist of the lacrimal, with its watery secretion, the Harderian, with a probable fatty product, and the Meibomian glands. A histological study of these structures shows questionable changes in the lacrimal and Meibomian glands, and marked changes in the Harderian gland.

The changes in the Harderian gland are both degenerative and inflammatory. The degenerative changes consist of swelling, vacuolation, and occasionally complete epithelial disintegration. The inflammatory lesions may be either acute or chronic. The acute reactions are sometimes diffuse, but are more often focal. Definite suppuration occasionally results. The acute process generally passes over into a chronic inflammation with mononuclear cell infiltration, fibrosis, and atrophy. The changes demonstrated indicate a serious disturbance in the secretion of the Harderian gland, such as may conceivably render the conjunctiva susceptible to infection.
These studies suggest the importance of investigating the paraocular glands in other types of conjunctival infection. It is possible that they may have a definite relation to the origin and course of such infections.

We wish to express our indebtedness to Miss Eunice E. Chace, of the Department of Zoology of Smith College, for references and other data respecting the anatomy of the lacrimal and Harderian glands.

EXPLANATION OF PLATES.

PLATE 7.

Fig. 1, a and b. (a) Lacrimal gland. (b) Harderian gland, showing the close relation of the two structures and the normal histology of each. Many of the acini of the lacrimal gland show no lumen, whereas the lumina of the acini of the Harderian gland are comparatively large. × 100.

Fig. 2. Harderian gland showing comparatively normal acini. The free margins of the cells are ragged. The lumina contain yellow, granular precipitate. Zenker fixation.

PLATE 8.

Fig. 3. Harderian gland showing parenchymatous changes. The cytoplasm of the cells is ragged and contains numerous vacuoles.

Fig. 4. Rat with advanced ophthalmia. Necrosis of epithelium involving one lobule of the Harderian gland.

PLATE 9.

Fig. 5. Rat with well marked ophthalmia. General dilatation of the acini of the Harderian gland. × 100.

Fig. 6. Suppurative inflammation of the Harderian gland. The tubules are filled with disintegrating polymorphonuclear leucocytes.

PLATE 10.

Fig. 7. Old rat with chronic conjunctivitis. Diffuse chronic inflammatory process in the Harderian gland with dilatation of the ducts, atrophy of the acini, marked increase in connective tissue, and widespread mononuclear cell infiltration. × 100.

Fig. 8. Complete atrophy of a lobule of the Harderian gland with replacement by fat and connective tissue. × 100.
FIG. 1.

FIG. 2.

(Lambert and Yudkin: Deficiency of vitamin A.)
(Lambert and Yudkin: Deficiency of vitamine A.)
(Lambert and Yudkin: Deficiency of vitamin A.)
Fig. 7.

Fig. 8.

(Lambert and Yudkin: Deficiency of vitamin A.)