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The origin of the primordial droplets has been rightly given the primary place in the study of secretion. Bowen has limited the term secretion to the actual synthesis of these droplets from cytoplasmic materials, which limitation we shall accept. The secondary problems in this field concern chiefly extrusion or storage of these elaborated secretions. While we shall review the literature concerning goblet cells in both fields, our contributions will lie for the most part in the secondary field.

The molluscan material used in this study is from several hundred slides made by the author. The material on the spiny dogfish embryo is from a study of some forty slides made in 1931 by students at the University of Utah, which chanced to show the features concerned remarkably well. Other slides from various sources have been used. Methods of preparation for the first have already been given in the author's 1935 paper. In this study the author has appreciated the facilities of the Zoology Departments of both Utah and Indiana universities and is indebted to the teaching staff at both institutions. The library facilities of the Indiana University School of Medicine have also been freely used.

Before reviewing the literature on the goblet cell, let us critically glance at some current ideas in the general field. Bowen, just before his untimely death, rejected Ranvier's classification of glands into the holocrine, intermediate, and merocrine types as superficial; and substituted Renault's classification, into plasmocrine and rhagiocrine as more suitable. For those unfamiliar with the field it might be briefy explained (fig. 1) that a holocrine gland, such as a sebaceous (oil) gland of the human scalp, actually extrudes cells containing secretion droplets; an intermediate or apocrine gland, like the mammary gland eliminates only the broken-off, peripheral expansions of the cells with their elaborated milk droplets; while a merocrine gland, such as in pancreas, has the secretory products washed out from the individual cells which are left to repeat the process. In the plasmocrine mode of secretion, as Bowen explains, a vacuole forms and grows, but from the start it is completely filled with homogeneous material, fluid or semi-fluid in nature. In the rhagiocrine type of secretion a similar vacuole appears in which a granule of the secretion soon becomes apparent, which eventually grows to fill the relatively more slowly expanding vacuole.

Bowen held that Ranvier's classification had little significance since eventually individual cells of the merocrine type also wear out and go to pieces or are lost in glandular products and their places are taken by new cells. In other words each type of cell eventually goes through the same cycle. To him Renault's classification seemed fundamental since it concerned the primary problem, the elaboration of the secretion. Ranvier's classification, however, seems far from superficial when viewed from the admittedly secondary field of excretory or storage activities of the cell. When we consider the immediate environment or "neighborhood" of the cell, the fact as to whether it "moves out" or becomes a "useful resident" of the community of cells composing that tissue, has far more than a "sociological" significance, for there must be physiological factors which cause the former to "let loose". Whether its protoplasm is so overgorged with secretion droplets that it is unable to "unload", or whether its basal membrane or intercellular substance holds it less efficiently than that of the merocrine cell, or whether its intracellular secretory apparatus is less durable to the wear of continued activity, or whether it is shed sooner because of starvation from a poorer nutritional supply, are all important physiological possibilities which may be of great significance. The fact that they lie neither in the field of cytology, the study of the cell, nor in the field of histology proper, the study of the arrangement of the cells to form the various tissues, should not minimize their importance as physiological borderline cases. We shall have more to say later about the merocrine nature of goblet cells.

Goblet cells are generally regarded as unicellular merocrine glands which secrete mucus which is contained in an intracellular reservoir of such capacity as to bulge the side of the cell outwardly. The name was first applied in mammals where the fully developed cell has a strikingly chalice-like form, consisting of a slender basal stalk and a bulging apical portion, the latter containing the oval reservoir of mucigen which often protrudes into the lumen as a frothy plug. Maximow and Bloom state: "Mitoses have been observed occasionally in them. As a rule, however, new goblet cells arise through a transformation of indifferent epithelial cells or cells with a striated border or cilia. The transformation of a goblet cell into a common epithelial cell seems doubtful." Scott and Kendall describe the process of secretion of goblet cells as follows: "Mucin, which is elaborated in the cytoplasm of these cells, collects toward the free end, water is absorbed, and the volume of the secretion is increased so that the apical end becomes much distended.

The distension progresses until there remains so thin a sheath of cytoplasm about the secretion that a rupture occurs and there is a discharge of the mucus." Bremer regards the rupture of the "top-plate" as an artifact, at least in some cases. "In the mucous cells of the intestine, secretion is formed below and discharged from the free surface at the same time." He cites the contrast in regard to salivary mucous cells, which apparently remain filled with mucus continuously, presumably discharging the mucus as rapidly as it formed. He intimates that the enlarging of the cell is due to the secretion being formed faster than it is discharged, and vice versa. Bremer does not apply that principle to the goblet cell as does Addison who states that "when the distension becomes too great, the cell ruptures in the direction of least resistance and the secretion is poured out upon the surface of the mucous membrane as the lubricating mucus." Maximow and Bloom state: "The droplets of mucigen leave the goblet cell through the opening on the surface, dissolve at once and are transformed into mucin. This elimination of mucigen may proceed gradually and the cell may keep its goblet form for a long time. In other cases the whole content is thrown out at once and the emptied cell collapses and is compressed between the neighboring epithelial cells. After a while a new accumulation of mucigen may begin in the same cell."

The earlier figures showing the origin of mucus in the goblet cell attempted to show the formation of the reservoir around some structure. The first edition of Maximow and Bloom (fig. 38) redrew one of Zimmermann's figures showing three goblet cells, each with one diplosome in the center of the mucus-filled reservoir. E. B. Wilson reproduces a figure (fig. 22) from Cajal that shows the reservoir developing around and distal to the Golgi apparatus, which apparently is breaking into secretion granules in the reservoir from which the secretion will presumably be elaborated. Bowen, whose figures are also reproduced by Sharp (fig. 37), gives the current concept, that the secretory droplets arise on the strands of the Golgi net. The droplets pass from this meshwork toward the distal region of the cell, where they coalesce to form the reservoir. "As they move away from the net each is seen to have a small chromophilic cap or girdle" probably of Golgi material as the "gradual disappearance of this girdle as the droplet enlarges suggests actual transformation of the Golgi substance into secretion". Kaywin has recently published observations as to the relation of secretion droplets to Golgi substance in cells of the intestine of the tadpole of *Rana catesbiana.*

In our studies of the embryonic skin of the spiny dogfish (fig. 2C), goblet cells were found occurring abundantly in the stratified squamous epithelium just above the Malpighian layer from which they probably arose. They were of the spherical type rather than the chalice-shaped. Considering the side of the cell toward the basal membrane as proximal, the flattened nuclei were crowded against either the proximal or lateral portions of the cell, never against the distal.[1] Most of these goblet cells occurred in the middle or polyhedral layer, though a few had pushed through the squamous layer to the free surface. In such cases the squamous cells seem to be parted or pushed aside by the migrating goblet cell, the base and sides of which are still surrounded by polyhedral cells. The flattened nuclei of these goblet cells would seem to imply no connection with the basal membrane, though this cannot be verified from the preparations studied.

In mammalian tissues (fig. 2A and B) goblet cells are ordinarily found only in simple epithelia where their secretions are spread over a free surface. Bremer explains that "in certain stratified and pseudostratified epithelia the formation of mucus has been seen to take place in some of the deeper cells but the discharge of the secretion can occur only when these cells have reached the free surface". The goblet cells in the embryonic dogfish skin seem not to be involved in the enamel organ tissue that is differentiating over mesodermal scale papillae. They occur in the epidermis between these regions of scale formation.

The types of unicellular glands that Bevelander describes from the branchial epithelia of fish, provide interesting comparisons with the above-described goblet cells from the skin. Especially interesting is his figure 3 from *Protopterus*, as it approximates a mammalian goblet cell, yet it is so large and so elongate as to extend practically throughout the thickness of the stratified epithelium in which it occurs. It is almost intermediate between the goblet cells we have been studying, and those we shall now consider, which are enormously elongated structures, which, though retaining their connection with the epithelium from which they are derived, sink deep into the dermal tissues beneath. They are usuallyy known as subepithelial glands.

[1] Dr. H. M. Smith, in an article that unfortunately has no bibliographic references, has described in shark skin these same structures as "simple sac-like glands each lined with a layer of flat cells opening to the surface". His figure would lead to the conclusion that they are multicellular glands as in Amphibia. Our material very clearly shows a unicellular gland with clasping polyhedral cells, somewhat as figured by him in the gland shown near his median label Sc. Reexamination of our slides, however, shows also very clearly the fine lining cells described by him. When both these and the nucleus are cut through, the nucleus lies inside, which would indicate to me that they are probably sheath cells. However, as I have not seen Dr. Smith's material and as the material which I have studied is limited in amount, other possibilities might exist (e. g. a developmental sequence of unicellular, multinucleate, and multicellular phases) though I do not believe such is probable in this case. Smith, in the same article, describes unicellular mucous glands in the squamous epithelium covering perch scales.

Two great groups possess subepithelial glands: in the vertebrates, the Amphibia; in the invertebrates, the Mollusca. The former are multicellular in nature, as described by Miss Muhse (see our fig. 3A) and various other authors. The latter are unicellular though often much larger than the multicellular ones in amphibians. In the pedal epithelium of the fresh water mussel there is only one type, an elongate mucous gland. In snails, however, there are many types, some mucous, some albuminous, some with calcareous particles, and some with liquid pigment. Both (fig. 3B and C) have been dscribed by the author, the type in mussels in a paper dated 1925-27, the types in snail mantles in the article dated 1935. Of the many kinds found in snail mantles we shall be concerned with only the mucous glands, of which there are two, a large and a small, that exhibit many differences besides size. In examining over one thousand slides of approximately thirty species of North American snails, I have yet to find a mucous gland in the mantle multinucleate, though I have reported a few rare instances of such a condition in albuminous glands. Both types of mucous glands occur also in the foot of snails. Also the large pedal slime gland that secretes the sticky roadway on which the snail progresses is of the mucous type (fig. 4). The large type of mucous gland has been present in the mantle and foot of every species examined. The small mucous gland has been identified in practically all, though in some mantles its presence is doubtful, in some cases due to insufficient material, in others due to difficulty in separating it from immature glands of the large type. The derivation of the large type of mucous gland from the parental epithelium can be easily traced in our North American snails (fig. 5) as Roth has done in the European edible snail, *Helix pomatia.* The mucous glands do not present the multiplicity of phases that are shown by the albuminous glands. However, their secretion seems to vary in consistency in a few cases with species, in many cases with the physiological condition when the animal was killed, and in practically all cases with the diversity of fixing agents and stains used. Therefore the appearance of mucus in the glands on any one slide does not mean much, unless one knows the above factors, or can in some way eliminate all but one of the above factors. Mucus rarely appears homogeneous, it often takes the form of a smear or of bubbles, but sometimes forms ropy fibrils.

Since in my 1935 studies, mucus was seen never to have been associated with shell production, but only with slime production, a check has been taken to see whether or not snails living in dry regions might not have more mucous glands than those living in exceedingly damp regions. No such correlation was found. The mantle and foot of

Polygyra from wooded bluffs skirting the open prairies of Iowa or *Vitrina* living in exposed canyons of isolated desert mountain ranges of Utah have apparently the same type and approximately the same relative number of mucous glands as has *Monadenia* from the misty Willamette Valley of Oregon or *Polygyra* and *Anguispira* from the humid river valleys of southern Indiana or Ohio. Even aquatic snails, e. g. *Physa,* have numerous mucous glands. Obviously the mucus in the slime is not to prevent evaporation, though it may slightly retard it. Snails of all areas withdraw into the shell and by opercula or by dead air spaces between epiphragms seal themselves from the fatal effects of excessive evaporation. It is more probable that the mucus in the slime serves as a lubricant to protect the simple columnar epithelium of the integument as it cannot be efficiently replaced when worn as can the exposed squamous layers of stratified squamous epithelium such as is found composing the integuments of most terrestrial animals. This seems more probable since it is those parts of the mantle that rub against the body as the snail emerges from or retracts into the shell, and those parts of the foot that encounter external friction, that have the most copious supply of mucous glands. The goblet cells in the simple columnar epithelium of the epidermis of the earthworm would seem to protect it similarly from the friction of its burrow. The foot of the fresh water mussel similarly has its simple columnar epithelium lubricated, apparently to protect it from the friction of the sand through which it burrows.

Furthermore, secretion in mucous glands in snail mantles proceeds to the limit, not under conditions of dryness and high temperatures, but under conditions of high relative humidity and high temperatures. In the former case the snail withdraws within its shell and dies apparently because of desiccation without much production of slime. The latter condition was tested in a series of as yet unpublished preliminary experiments on the optimal and survival temperatures, humidities, and barometric pressures of Indiana tiger snails. It is not my purpose here to describe these experiments, nor the resulting tendencies that were indicated, nor the controls examined, but only to report the histological condition of three snails out of forty, the only survivors in saturated flasks that were kept at a temperature of approximately 37 degrees Centigrade for a period of five days. When the mantles of these were sectioned, all structures appeared normal except the mucous glands, which were shrivelled in size but more globular in shape. Where the mouth of these was sectioned, the mouth was seen to be wide-open instead of narrowly constricted as normally. In fact, the whole mucous gland sometimes protruded almost from the mantle (fig. 6). This suggests that temperature might be a factor in inducing holocrine tendencies in exhausted merocrine glands of the unicellular type.

Some snails have developed a mesodermal expulsive mechanism around the large mucous glands only. *Polygyra thyroidus* shows this developed to the greatest degree in the mantles so far examined (fig. 7). It is shown to a lesser degree in *Discus* (*Anguispira*) *alternatus* and also in *Helix pomatia*. In others examined it can scarcely be said to be more than a pushing aside of muscle fibers by the enlarging mucous glands. In the above three, however, the association of muscle fibers and the wall of the unicellular gland seems too intimate to be merely incidental.

To summarize: (1) Ordinary goblet cells, which are largely confined to simple columnar and pseudostratified epithelium in mammals, are found in stratified squamous epithelium in the epidermis of spiny dogfish embryos in regions between developing scales. (2) The unicellular mucous glands of fresh water mussel and snail represent subepithelial downgrowths of differentiating epithelial cells. They are actually ultra goblet cells, so large that they expand far into the dermal tissues below the epithelium in which they originate. (3) Comparative studies of land snails from dry and moist regions indicate no appreciable variation of mucous glands correlated with regional humidity. (4) This, with the fact that aquatic snails also have mucous glands that contribute to the slime, makes it seem probable that mucus more probably serves as a lubricant, rather than as a protection against evaporation.[2] (5) Temperatures at 37 degrees C. maintained over several days selectively exhaust mucous glands even when relative humidity is absolute.[3] (6) the large unicellular mucous gland in snails may possess a mesodermal mechanism of muscle fibers which may serve in the expulsion of its contents.

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[2] The lubricatory function of mucus may in mammals have some exceptions; e.g. stomach mucus may possibly protect against alcohol.

[3] Montgomery and Stuart whose publication appeared after this article was finished, state from another angle. "During periods of water deprivation the mucous glands maintain their normal rate of secretion longer than do the salivary glands."

Plate I

Figure 1. Ranvier's types of secretion.

A. Holocrine secretion as illustrated by follicle of human Meibomian gland. See also Fig. 6.
   - *c.* Cell being secreted.
   - o. Oil droplets.

B. Apocrine type of secretion as illustrated by cells from human mammary gland.
   - *a.* Apical portions of cells being secreted.
   - *m.* Milk droplets.

C. Glandular epithelium from human cardiac stomach illustrating merocrine secretion into the central lumen (1).
   - *c.* Chief cell.
   - *p.* Parietal cell.

Figure 2. Types of goblet cells or intraepithelial mucous glands, as contrasted with subepithelial mucous glands as shown in figures 3 to 7.

A. Usual shapes of goblet cells (g) as found in simple columnar epithelium of human colon.

B. Pseudostratified epithelium of trachea of cat, illustrating usual shapes of goblet cells (g). The goblet cells do not bear cilia, but as this slide was cut at 10 micra, ciliated cells behind the goblet cells showed.

C. Cross section of the embryonic skin of the spiny dogfish, *Squalus acanthias* L., cut at 60 micra. The thick sections sometimes show the nucleus (n) of a goblet cell (g).
   - *p.* Pigment cells.
   - *m.* Malpighian layer.
   - *s.* Squamous layer.

Figure 3. Types of subepithelial mucous glands.

A. Multicellular glands (g) in a cross section of the skin of the frog, *Rana palustris* Le Conte. Locality—Jordan River, Indiana University Campus.
   - *b.* Beaker cells—unicellular exuvial glands.
   - *f.* Fat cells.
   - *m.* Malpighian layer.
   - *s.* Squamous layer.
   - *e.* Epidermis.
   - *d.* Dermis.

B. Subepithelial mucous gland (m) in the pedal epithelium of the mussel, *Tritogonia verrucosa* Raf. (*T. tuberculata* (Barnes)). Locality—Iowa River near Iowa City.

C. Subepitheial glands in the mantle epithelium of the land snail, *Polygyra andrewsae normalis* Pilsbry. Locality—Mt. Kephart, Great Smoky Mts., Tenn.—N. C. border. O. D. Mc Keever, Collector. Slide 419.
   - *m.* Mucous glands.
   - *a.* Albuminous gland.
   - *n.* Nucleus.

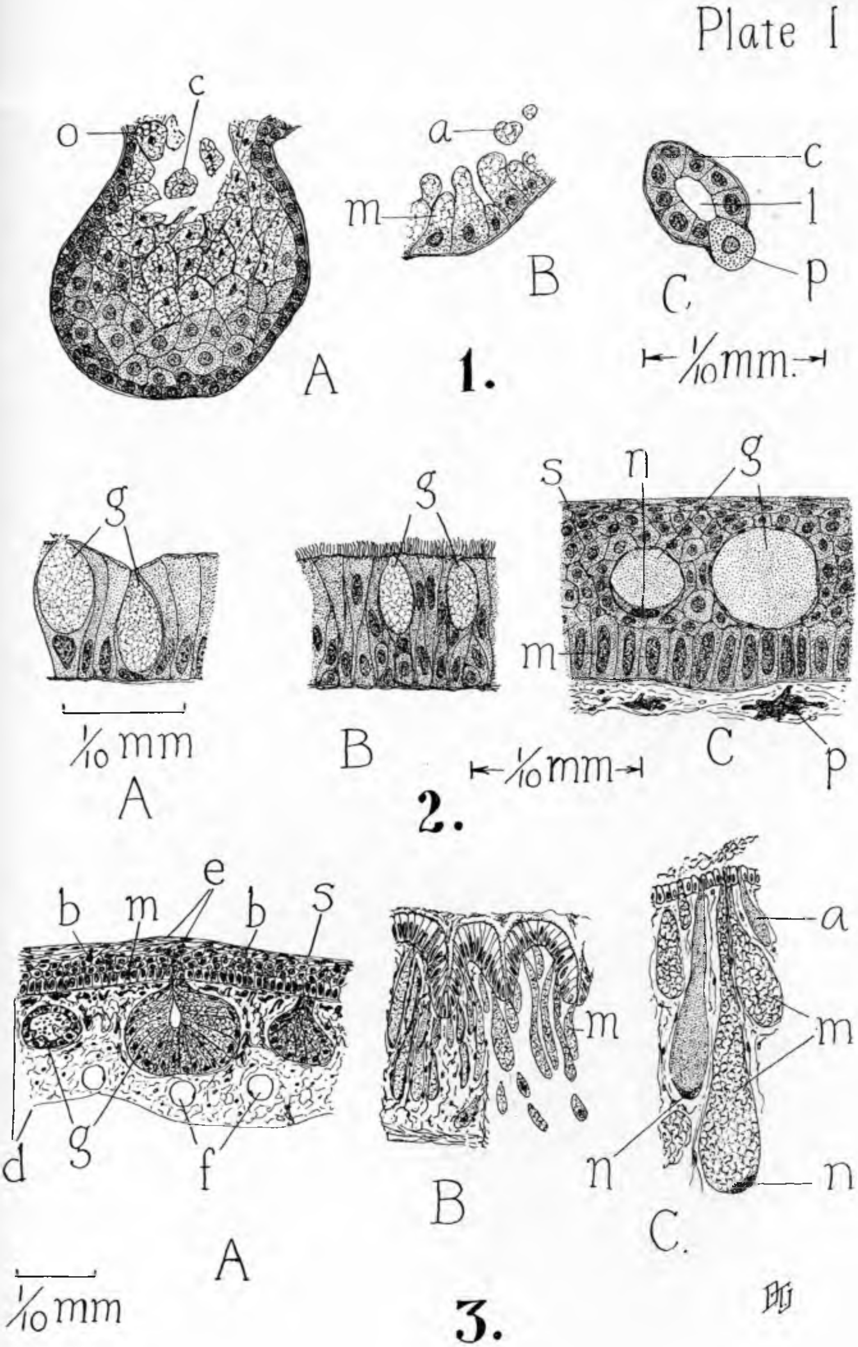
Plate I
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Plate II

Figure 4. The pedal slime gland (p), a group of unicellular mucous glands of the small type, opening into a common duct (d). From a cross section of the foot of a juvenile tiger snail, *Discus* (*Anguispira*) *alternatus* (Say). Locality—Indiana University Campus. Slide 296.

g. Unicellular mucous gland of the integument.

m. Muscles.

Figure 5. Derivation of both large (l) and small (s) mucous glands from the parental epithelium. From the front of the mantle of the land snail, *Polygyra palliata* (Say). Locality—Coon Cave, near Bloomington, Indiana. Julia Frazier, Collector. Slide 89.

a. Albuminous gland.

g. Supramarginal groove.

r. Supramarginal ridge.

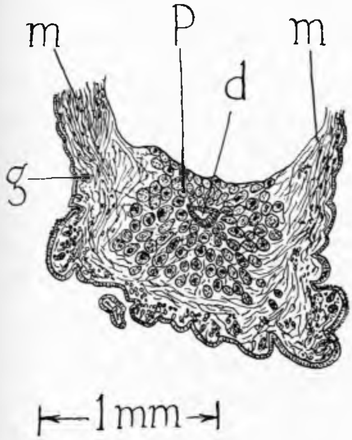
Figure 6. Section of the mantle of *Discus alternatus* (Say) after the snail had been subjected to a constant temperature of 37 degrees C. for a period of five days. Note the wide open mouth (m) of large mucous gland, also the holocrine tendency (h) of these glands to shed the single cell that composes the entire gland. The albuminous glands (a) remained normal. Locality—Indiana University Campus. Slide 317.

Figure 7. Large mucous gland from the mantle of the land snail, *Polygyra thyroidus* (Say), showing gland musculature (m). Locality—University Dam, Bloomington, Indiana. Stacey Denham, Collector. Stain-Iron hematoxylin. Slide 273.

a. Albuminous gland.

o. Openings of mucous glands.

Plate II



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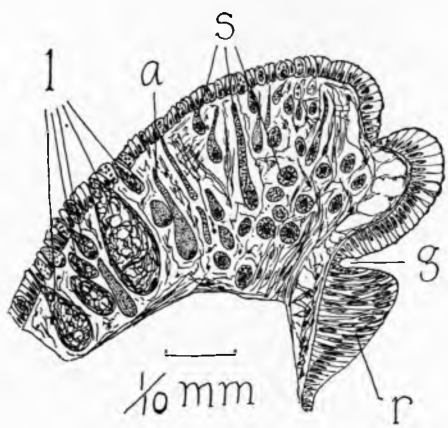

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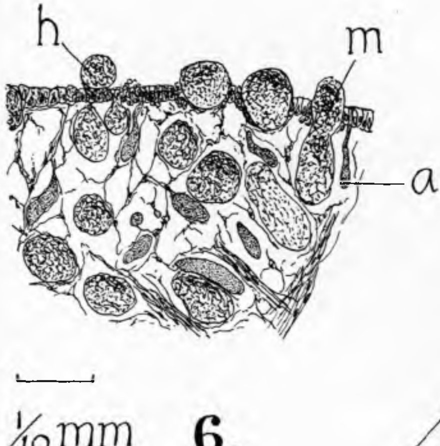

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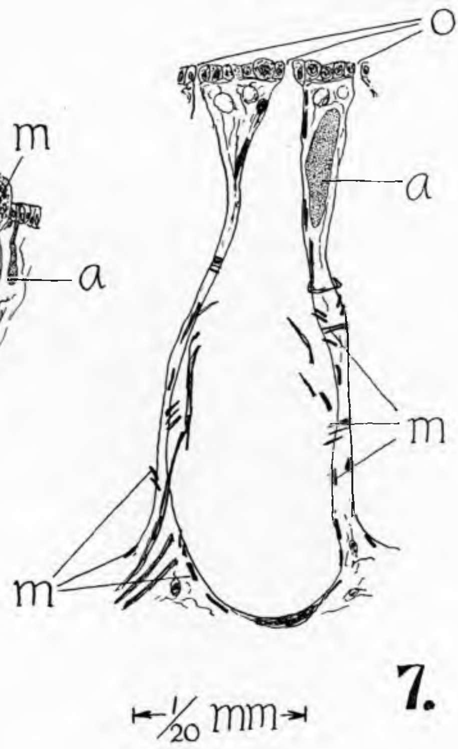

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