Abstract. Because cone outer segments (COS) are now known to be continually renewed, I reexamined COS morphogenesis in retinas of *Xenopus* tadpoles (prepared by standard histologic techniques and viewed by light and electron microscopy) to clarify how COS incorporate new membrane. I observed that developing COS underwent an unexpected shape change: they were always conical, but their taper (width divided by length) continually decreased. Ultrastructural examination revealed that many of the membrane foldings within distal COS were partial or incomplete, not extending across the full COS width but ending at variable distances from the ciliary side. Because these partial folds represented infoldings of the plasma membrane of an existing lamella, and they occurred at all COS levels except the base, I have termed them distal invaginations (DI). The completion of each DI increased COS length by one lamella but caused no noticeable change in local COS width; thus the formation of many DI throughout the distal COS presumably resulted in the observed decrease in overall COS taper. Based on these findings, I suggest that DI indicate growing membrane fronts and may represent sites where newly synthesized membrane is incorporated into COS. Because DI occur in developing and adult COS of various vertebrate species, I propose that DI formation plays an important role in the generation of COS taper during development and the remodeling of COS taper in mature cones after tip shedding.

Although it is now accepted that the light-sensitive outer segments (OS) of both vertebrate rods and cones are regularly renewed (Anderson et al., 1978; Young, 1978; Bok, 1985; Roof, 1986), numerous aspects of cone outer segment (COS) renewal remain problematical. I have reexamined the morphogenesis of COS to clarify how new membrane is incorporated into COS.

Rod outer segment (ROS) membranes are renewed in a very orderly manner, as first revealed by autoradiography (Young, 1967): radioactive protein molecules become trapped in new membranous disks generated at the OS base, producing an autoradiographic band of label; the unchanged band is displaced sclerally as additional disks form below, and finally discarded from the OS tip and phagocytized by the pigment epithelium (Young and Bok, 1969). This pattern of membrane renewal is consistent with the ultrastructural morphology and cylindrical shape of mature ROS (Young, 1976; Steinberg et al., 1980; Bok, 1985). It is thus clear how new membrane is incorporated into ROS: each membrane entering via the connecting cilium becomes distributed into successive new membrane folds that evaginate from the ciliary membrane and are displaced away from the base, then lose their connections and become isolated into separate disks surrounded by the plasma membrane.

COS differ from ROS in structural organization, autoradiographic labeling pattern, and three-dimensional shape. COS likewise consist of numerous parallel membrane foldings oriented at right angles to the connecting cilium, but in COS all the membrane foldings apparently retain continuity with each other and with the plasma membrane, forming a single topologically continuous membrane system. To emphasize the topologic distinction between ROS and COS membranes, I will refer to the cytoplasm-enclosing membrane foldings in COS as lamellae, rather than disks. Thus, although different COS vary in external form, their membranes are believed to have the same structural organization (Young, 1970; Fein and Szuts, 1982; Papermaster and Schneider, 1982; Bok, 1985), illustrated in Fig. 1.

Autoradiographic experiments produce a diffuse labeling over COS, which was originally taken as evidence that they undergo no analogous membrane renewal (Young, 1969): when COS attained their final size, the addition of new membrane was believed to stop. The tapered conical shape of COS was taken as circumstantial evidence that their membranes are not renewed (Young, 1969), and attributed (Young, 1971) to the way they form during development (Nilsson, 1964): the earliest membrane foldings are small and successive folds formed below become progressively larger.
membrane renewal was questioned in subsequent studies. It apparently added by sclerad flow of the ciliary membrane at the OS base (Kinney and Fisher, 1978b; Holtzman and Mer-
Results

LM Observations of COS Shape

COS development was rapid. Initial COS outgrowth occurred at the beginning of the present experiment, and COS grew to their full adult dimensions (Kinney and Fisher, 1978a) during the following 3 d. Shedding of OS tips had likely not yet begun, in that phagosomes were never found in the pigment epithelium, and the tips of all longitudinally sectioned OS were clearly pointed, rather than truncated.

Light micrographs of COS on experimental days 1–3 are shown in Fig. 2. COS had circular cross-sectional profiles (determined from tangentially sectioned COS in the first LM sections cut into the eye), straight sides, and pointed tips (determined from longitudinally sectioned COS in the posterior retina). Accordingly, I approximated the shape of developing COS as a pointed circular cone, and derived a generalized COS outline at each time from LM measurements of COS dimensions.

A comparison of COS shape on successive days (Fig. 3) yielded a surprising finding: although COS were always conical, they became relatively thinner with time. Thus, when COS outlines on different days were superimposed on top of one another at the tip (first composite drawing in Fig. 3), the angle formed at the COS tip decreased each day: the lamellae at the COS tip seemed to be shrinking. Because COS maintained a smooth external outline, COS width was apparently decreasing at all distances from the tip: all preformed lamellae seemed to be shrinking. If COS shape is quantified as COS taper (the taper of a simple cone equals the ratio of basal width divided by length), the taper of developing COS decreased daily. This finding is inconsistent with the current model for membrane incorporation into photoreceptor OS. If all membrane entering a COS flowed into successive BE, before tip shedding the width of individual preexisting lamellae, COS width at a given distance from the tip and COS taper should not change.

EM Observations

Spacing and General Appearance of COS Lamellar Membranes. One possible explanation for the change in COS shape is that lamellar spacing changes during development. I examined developing COS by EM but found no systematic changes in their membranes. COS lamellar ultrastructure was similar at all heights and at all times. COS membranes were arranged in an orderly array: they were largely flat and parallel to one another, with on average 45 double lamellae per micrometer of COS height and no significant variation with time ($P = 0.05$ by the $t$ test).

Asymmetry between Ciliary and Nonciliary Sides of COS. Another approach to understanding the observed COS shape change is to take the base of the connecting cilium as the point of reference. When the outlines of developing COS...
Partial Foldings in Distal COS. Additional EM observation revealed that small irregularities were consistently present in the otherwise very regular COS membrane array (Figs. 5 and 6). At such sites, adjacent membranes were more widely separated than usual, producing an expanded pocket of cytoplasm. Upon actually following the course of the membrane at such locations, I realized that each marked the edge of an incomplete or partial membrane folding. Whenever the connecting cilium (identifiable by the ciliary axoneme, matrix, and/or membrane) was evident at the same COS level as such a partial folding, the partly formed fold extended from the nonciliary side of the COS and ended at such a spot. Based on their orientation with respect to the cilium, such partial folds were not invaginations of the ciliary membrane but infoldings or invaginations of the plasma membrane opposite the cilium.

In many cases these partial distal folds occurred singly, but sometimes up to 10 of them were observed next to each other, with no intervening complete folds. I found examples of such partial folds that ended at all possible positions between the ciliary and nonciliary sides of the COS (Figs. 6 and 7).

Partial folds with this orientation were found in all developing COS examined, and represented ~8% of the total lamellae per COS (Eckmiller, M. S., unpublished observations). They occurred with similar frequency at all distal COS heights, from the tip region down to near the base.

Suggested Terminology: DI. Because such partial membrane foldings were found throughout all nonbasal, i.e., all distal, levels of COS and represented invaginations of the plasma membrane, I have termed them "distal invaginations" (DI).

Features of DI. The presence of individual DI led to minimal interruption of the regular spacing between COS lamellae; larger groups of partial foldings produced a greater disruption of the membrane array (Fig. 6), so the completed lamellae immediately above and below a series of incomplete folds were not parallel to one another but separated by a considerable distance on the nonciliary side.

After extensive ultrastructural observations, including three-dimensional reconstruction of DI fronts in serial EM sections (Eckmiller, M. S., unpublished observations), I derived the presumed steps in DI growth (Fig. 8). A DI arose as a tiny infolding or indentation in the nonciliary edge of a preexisting COS lamella and expanded within that lamella by growing symmetrically towards the connecting cilium. The growth of a DI was completed when it reached the cilium, whereupon one preexisting lamella had been divided or split into two daughter lamellae resembling their predecessor in size, shape, and membrane spacing: the two daughter lamellae were indistinguishable from the other COS lamellae.

DI were not confined to developing cones or the cones of lower vertebrates: at the end of the present experiment COS had attained their mature dimensions, and analogous partial foldings were found in COS of adult Xenopus and macaque retinas (Eckmiller, M. S., unpublished observations).

Discussion

COS Taper Decrease during Development

An interesting new observation made in the present study is that the taper of developing Xenopus COS decreases: the ex-
ternal shape of an entire COS is continually remodeled or reshaped, as a unit, from the time of its initial outgrowth until its mature form is attained. Because there are no indications that COS development in *Xenopus* is unique, systematic observation will likely disclose a similar taper decrease in the developing COS of other vertebrates.

The observed mode of COS growth cannot be reconciled with either the previous explanation for the tapered shape of COS (Young, 1971) or the current model for membrane addition to OS by the formation of successive BE (Steinberg et al., 1980). It has been proposed (Steinberg et al., 1980) that mature COS are tapered because their distal lamellae shrink by somehow losing membrane; from the perspective of the COS tip, the present findings imply that lamellae of developing COS likewise shrink.

Another way of viewing COS morphogenesis is to take the connecting cilium, rather than the OS tip, as the reference point. When COS outlines from successive days are superimposed at the OS base by the connecting cilium, the change in taper of developing COS can be interpreted as reflecting a differential growth, which cannot be accomplished solely by adding new evaginations to the COS base.
Figure 5. Example of a developing COS in which the stack of membrane foldings contains numerous inhomogeneities, where adjacent membranes are slightly separated from one another by a small wedge of pale cytoplasm; closer inspection shows that these locations mark the edge of incomplete membrane folds (white arrows). (C) Connecting cilium. Bar, 0.5 μm.
**Ultrastructural Findings**

Lamellar spacing in *Xenopus* COS did not change during development, but the alignment of adjacent fold margins differed on the ciliary and nonciliary sides of the COS, as expected if the cilium is the main channel for membrane flow.

A significant new ultrastructural finding is that COS membranes contain partial DI. Partial membrane foldings are typically found at the base of all vertebrate OS (BE), but have not been previously described within distal COS. I have observed DI in developing and mature *Xenopus* cones, and in adult monkey cones. Similar partial infoldings within the distal COS can be seen in published electron micrographs of retinal cones from vertebrates as varied as frogs (Fig. 13 in Bok and Young, 1972) and squirrels (Figs. 1, 2 B, and 8 A in Anderson et al., 1978), as well as in conelike photoreceptors of the amphibian pineal gland (Fig. 1 in Kelly and Smith, 1964) and frontal organ (Fig. 1 in Eakin, 1961). Because DI are present in the COS of such a variety of vertebrates, I suggest that they are a general feature of vertebrate COS, whose significance has not been previously appreciated.

**Revised Model of COS Structural Organization**

These ultrastructural findings have been incorporated into a revised representation of COS structural organization, illustrated in Fig. 9. The COS in the previous drawings (Fig. 1) has been modified so as to demonstrate that the adjacent fold margins are irregularly aligned on the ciliary side of the COS, and to include three DI. For reasons given above, the COS membrane organization shown in Fig. 9 is probably applicable to vertebrate cones in general, although it may require modification for mammalian cones (Anderson et al., 1978; Carter-Dawson and LaVail, 1979).

DI resemble BE in being incomplete membrane foldings that are presumably growing to the ciliary, or nonciliary side of the COS, respectively (arrows in Fig. 9); completion of a DI or a BE increases COS length by one lamella. DI differ from BE in several important respects. BE are lamellae that are restricted to the extreme base of the OS, arise in succession as evaginations directly from the ciliary membrane, and grow by expanding away from the cilium. By contrast, DI are distributed either individually or in multiples throughout...
Figure 7. A developing COS with a very short infolding of the membrane at the nonciliary edge of a lamella (arrow and inset); even at such a small infolding, the usual intracellular membrane to membrane spacing is retained. (C) Connecting cilium. Bar, 0.5 μm.

all OS levels except the base, and are not lamellae, as such, but invaginations that arise and grow within preexisting lamellae.

Explanation for Asymmetry in Vertical Alignment of COS Margins

Opposite the cilium, adjacent fold margins are regularly aligned because they form part of the external COS outline and are supported by cytoskeletal elements (Fetter, 1984; Usukura and Bok, 1985); the ciliary margins lie within the COS interior (see Fig. 9) and apparently receive less structural support.

The observed irregularity in vertical alignment of the ciliary margins of adjacent COS folds can also be understood as a manifestation of DI formation. Because a substantial proportion of Xenopus COS lamellae contain DI at a given time, all lamellae will become repeatedly split before they arrive at the tip and can be shed. All distal COS lamellae are thus potentially involved in DI formation, and the irregular alignment of the fold margins on the ciliary side of COS likely reflects a variability in the extent to which different DI have completed growing: an infolding that extends across the full width of the COS foldings is a DI that has grown to completion, slightly narrower foldings are DI that are less complete.

Hypothesis: DI Formation and COS Taper

I propose that the decrease in taper observed in developing Xenopus COS is a result of DI formation and, by analogy, that in vertebrate retinal cones and extraretinal conelike photoreceptors, DI formation plays an important role in the generation of COS taper during development and the maintenance of mature COS taper after tip shedding.

The proposed role of DI formation in modifying the taper of developing Xenopus COS is well supported by the present findings: a decrease in COS taper could not be accomplished solely by BE formation, but could result from the generation of new lamellae via DI formation.

As far as is known, new components are added to developing and mature COS by the same mechanism: a diffuse autoradiographic labeling is reported at both times, and BE are present in both cases. I have found DI in both developing and mature Xenopus COS, suggesting that DI formation occurs in a similar way and has a similar effect in both immature and mature COS. Because mature COS are generally narrower at the tip than the base (even primate foveal COS have a slight taper: Borwein, 1981), after shedding COS must become remodeled in order to regenerate a narrower tip (Bok, 1985). After shedding, the truncated shape at the distal end of COS could become narrower via DI formation, if in mature COS DI formation leads to a slight decrease in local COS width, i.e., if the two daughter lamellae produced by DI formation grow to slightly less than the full width of the preexisting lamella. The amount of tip narrowing achieved would depend on the relative number of DI vs. BE formed, and on how much DI formation decreased local COS width—any amount of taper (including a new pointed apex) could be
generated. A difference in the relative proportion of membrane flowing into new BE vs. DI could also account for the variable amount of OS taper observed in different cones—in highly pointed COS (e.g., those of Xenopus) relatively more membrane would enter DI, in less tapered COS more would enter BE.

Membrane Flow Routes within COS

The routes available for membrane flow within ROS are clear (Holtzman and Mercurio, 1980; Papermaster and Schneider, 1982): newly synthesized opsin molecules enter the basal outfoldings (Young, 1967) and the surrounding plasma membrane (Basinger et al., 1976); rhodopsin is capable of lateral

Figure 9. Revised drawings of the structural organization of COS membranes in (left) two and (right) three dimensions. Previous drawings (Fig. 1) have been altered to incorporate the irregular vertical alignment of the margins of adjacent membrane foldings on the ciliary side of the COS, and the presence of three DI; the retention of normal membrane spacing during DI formation is not indicated. BE grow away from the cillum (arrow to the right), DI grow towards the cillum (arrows to the left).
diffusion within the membranes of individual disks but not longitudinal transfer between different disks (Liebman and Entine, 1974). The membrane flow routes within COS are unclear, but the present findings provide a novel perspective for reevaluating this issue.

The splitting of one lamella into two lamellae during DI formation requires an approximate doubling of the amount of membrane present (see Fig. 8), whereby the membrane must flow into distal lamellae that contain growing DI. The additional material for a DI must enter the preexisting lamella at its only connection with the rest of the cell, namely over its narrow bridge to the connecting cilium (see Fig. 9); because membranous vesicles or tubules were not observed within the COS cytoplasm during DI formation, the membrane enters a lamella to form a DI by flowing over this bridge. Unfortunately, the morphologic findings of the present study do not specify the immediately preceding step, namely where the membrane that enters preexisting lamellae during DI formation comes from, which depends on how membrane flows within the rest of the COS.

Now that mature COS are known to incorporate new membrane, it is somewhat puzzling that a diffuse autoradiographic labeling is observed over COS. It is widely assumed (O'Day and Young, 1979; Papermaster and Schneider, 1982; Bok, 1985; Anderson et al., 1986; Roof, 1986) that new membrane is added to COS as BE, but that COS fail to display an autoradiographic band of label because protein molecules quickly diffuse throughout the fluid and topologically continuous COS membrane system. However, contradictory results have been reported regarding the rate of longitudinal diffusion within COS membranes (cf. Liebman and Entine, 1974, with Liebman, 1975), and new membrane molecules entering over the narrow cilium and moving into BE would have to travel a considerable distance before reaching the tip if they first had to move between all lamellae of the stack. Homogeneous distribution of all the new molecules throughout the COS could not occur instantaneously. If all membrane entering COS flowed directly into BE, autoradiograms prepared after very short survival times should produce a linear gradient of labeling over COS (high over the BE, decreasing gradually to a low at the tip), which has not been reported (heavier labeling over the basal half of COS has recently been observed: Anderson et al., 1986).

One very simple route exists for the flow of components within a COS: the cilium. Because it extends from the COS base to its tip and makes contact with each lamella, the cilium represents by far the shortest, most direct route for materials to move within the COS (see Fig. 9). Because newly synthesized membrane components enter an OS over the connecting cilium, membrane that originally entered the COS at the ciliary base must eventually travel sclerally within the COS to each of the various distal levels where a lamella becomes split by DI formation. A topologically simple possibility is for new membrane entering at the base of the cilium to flow directly sclerally, along the outer or eccentric face (Matsusaka, 1974) of the ciliary membrane to each COS level where a partial lamella is being completed, i.e., to each growing BE and DI (this would be similar to the flow of label into the plasma membrane of ROS [Basinger et al., 1976]). Thus, the membrane that flows into COS lamellae during DI formation could be either (a) preexisting membrane that has moved out of neighboring lamellae during redistribution of the membrane by diffusion throughout the entire fluid lamellar stack, and/or (b) newly synthesized membrane that has moved sclerally along the cilium. According to the second possibility, under certain experimental conditions autoradiograms might reveal a very specific distribution of label over COS. Label would first be restricted to the ciliary membrane, and then to several separate discrete lines parallel to the COS lamellae, corresponding to growing BE and DI (such lines of autoradiographic labeling have sometimes been observed over COS: see Results in Bunt, 1978; Eckmiller, 1986). After each DI completed growing, the two resultant lamellae would again be subject to splitting as additional DI formed, and each time this occurred their label would spread into all daughter lamellae; because DI are formed at all distal levels, a familiar diffuse labeling would soon extend over the entire COS. Although the second possible mechanism for membrane flow during DI formation is more likely because of its greater simplicity, the resolution of this issue must await further investigation.

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