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Morphogenesis of photoreceptor outer segments in the developing kitten retina

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INTRODUCTION

The aim of this study was to determine the sequence of photoreceptor outer segment formation in developing mammals. This sequence is known for amphibians from the studies of Nilsson (1964) and Kinney & Fisher (1978). At the base of the immature outer segment, horizontally orientated lamellae are formed from the plasma membrane and aggregate into a stack of ever increasing height. The formation of new lamellae also occurs in the mature photoreceptors of both amphibians and mammals (reviewed by Young, 1976). A new insight into this process was presented by Steinberg, Fisher & Anderson (1980), who proposed that new lamellae are formed by the evagination of a lip of plasma membrane outwards, away from the cilium. This leads to formation of a lamella which, in rods, detaches completely from the plasma membrane. However, there still remains the question of outer segment formation in developing mammals which, as described by Steinberg *et al.* (1980), suffers from the difficulties of obtaining good fixation and orientating the immature outer segments. Several proposals have been made. Tokuyasu & Yamada (1959), Ueno (1960, 1961) and Yamada & Ishikawa (1965) proposed that lamellae were formed from the coalescence of tubules, but this proposal is now of historical interest only. A more acceptable proposal involved the formation of lamellae by invagination of the plasma membrane (Sjostrand, 1959; McArdle, Dowling & Masland, 1977; Vogel, 1978*a*), but this was based on minimal evidence. The actual sequence of outer segment formation and the presence of randomly orientated lamellae, often of vertical orientation, as shown by so many investigators (De Robertis, 1956, 1960; Tokuyasu & Yamada, 1959, 1960; Weidman & Kuwabara, 1968; Hebel, 1971; McArdle *et al.* 1977; Vogel, 1978*a*, *b*; Greiner & Weidman, 1980, 1981) still require an explanation. These problems are investigated in the present study. Photoreceptor outer segment development in the kitten has been studied with conventional electron microscopy of retinae fixed with three fixation methods to check against fixation artefacts. Stereopairs of semithin sections were also obtained on a high voltage electron microscope to facilitate the three dimensional analysis of immature outer segments.

MATERIALS AND METHODS

These are described in more detail in an earlier report (Morrison, 1982). In addition to kitten retinae (ages 0–41 days), which were fixed in 1 % glutaraldehyde and 0·5 % paraformaldehyde in 0·05 M phosphate buffer, one newborn retina was fixed in 1 % OsO_4 in veronal acetate (after Dowling & Boycott, 1966), and other retinae (ages 0, 3, 5 and 13 days) were fixed in 4% glutaraldehyde and 4% paraformaldehyde in 0·1 M Sorensen buffer. Two adult rat retinae were also fixed in 2% glutaraldehyde in 0·1 M cacodylate buffer. One of these two retinae was fixed fresh and the other after 15 minutes had elapsed, to determine the effects of anoxia on outer segment structure. The retinae were sectioned on glass knives to give either serial ultrathin sections or single semithin sections, as previously described.

RESULTS

The present account places emphasis upon the description of the sequence of outer segment morphogenesis rather than the stages present at different ages, which are summarised elsewhere (Morrison, 1982). The account is based mainly on the development of rod outer segments, which were readily identified by their connection, via the cilium, to a compact inner segment with a nucleus which contained dense clumped chromatin. Cone outer segments, in contrast, occurred relatively infrequently, even in the area centralis. They were characterised by a large expanded inner segment and a pale nucleus which contained diffuse chromatin. It was mainly the area centralis which was studied, though outlying retina was also examined.

The outer segment developed as an expansion of the outer part of the cilium, which itself arose from the inner segment (Fig. 1). The outer segment progressively increased in volume and contained microtubules which arose from the cilium (Figs. 2, 3). Throughout development, the outer segments were very closely enveloped by processes of pigment epithelium which were surmised to play an important role, perhaps by facilitating the supply of nutrients from the choroidal circulation or by the release of trophic substances stimulating outer segment growth (Figs. 2–10). Often, processes of pigment epithelium were located in indentations of the outer segment's plasma membrane as if they were the cause of the indentations (Fig. 3). These usually occurred at the outer (sclerad) surface of the outer segment (Fig. 3) but were also seen on the lateral surfaces. This stage was followed by the occurrence of lamellae – double leaflets of membrane – inside the outer segment, which were continuous with the plasma membrane (Figs. 4, 5). So it was assumed that the indentations were the forerunners of the lamellae. In the course of development, many lamellae seemed to become detached from the plasma membrane, as shown by short series of ultrathin sections (Fig. 6), though the inference was never rigorously tested by sectioning through an entire outer segment. A major problem in this study was to establish where on the outer segment the lamellae were formed. This could be resolved only in radial sections which contained not only lamellae continuous with the plasma membrane but also the cilium to mark the long axis of the

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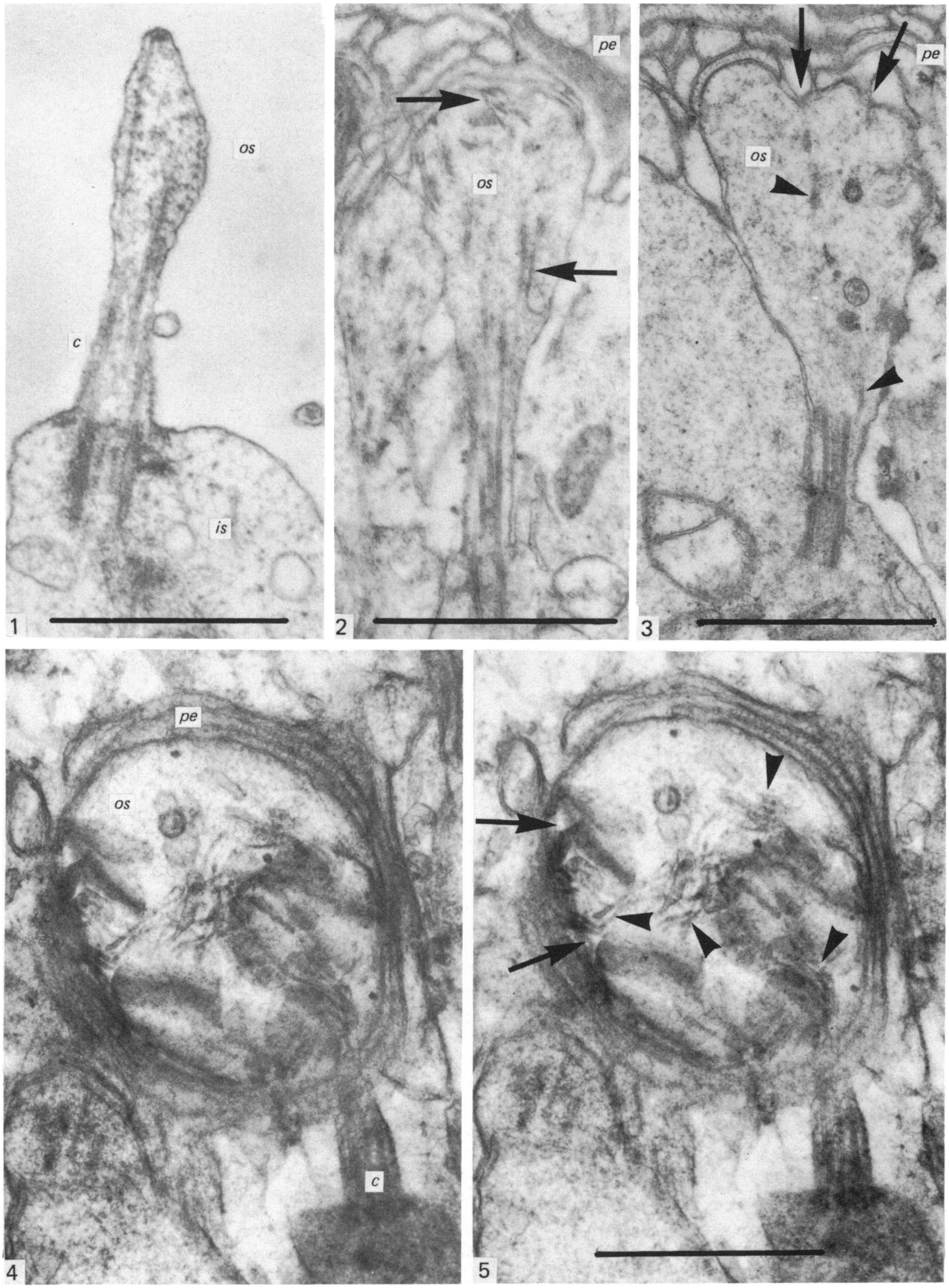
Fig. 1. Rudimentary rod outer segment (*os*) attached via cilium (*c*) to inner segment (*is*). Newborn kitten peripheral retina (detached from pigment epithelium). 1% glutaraldehyde. This and subsequent calibration bars, 1 μm.

Fig. 2. Small balloon-shaped outer segment (*os*) closely enveloped by pigment epithelium processes (*pe*) and containing microtubules (arrows). Newborn kitten area centralis. 1% glutaraldehyde.

Fig. 3. Larger outer segment (*os*) with indentations (arrows) at outer surface and presence of tubules (arrowheads). Newborn kitten area centralis. 1% glutaraldehyde.

Figs. 4–5. Stereopair of 0·25 μm sections, at 10° tilt, of radial section through an outer segment (*os*) with two lamellae continuous with the plasma membrane (arrows). Course of microtubules from cilium (*c*) may be followed into the centre, to a cluster of tubules (arrowheads). Newborn kitten area centralis. 1% glutaraldehyde.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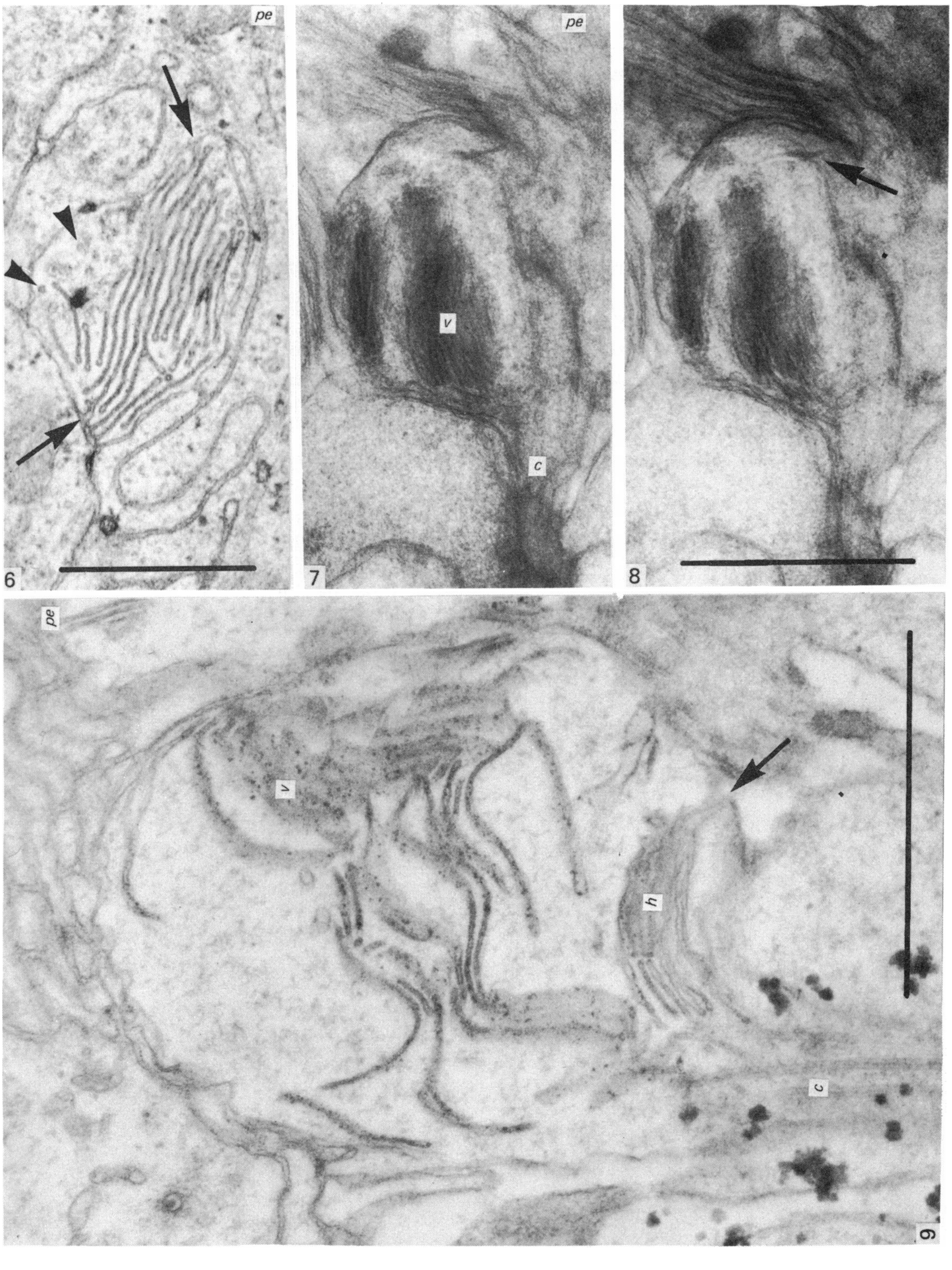
outer segment. To increase the probability of obtaining such sections, stereopairs of semithin sections were examined. The well developed outer segment in Figures 7 and 8 has a deep membrane indentation on its outer surface while the spherical outer segment in Figures 4 and 5 contains two lamellae continuous with the plasma membrane at its lateral surface. Figure 6 shows lamellae orientated parallel to the cilium and continuous with the plasma membrane on opposite surfaces of the outer segment. These observations suggest strongly that the lamellae were formed anywhere over the surface of the outer segment. This led to the formation of lamellae which had vertical or near-vertical orientations with respect to the long axis of the outer segment (Figs. 4, 5, 6, 7, 8, 9, 10). Less frequently, young outer segments which contained horizontal lamellae only were observed. In addition, the presence of microtubules and smooth reticulum in developing outer segments was observed in both ultrathin and semithin sections. In Figures 4 and 5, numerous tubules are shown as present in the centre of the outer segment, and appear to have arisen from the microtubules of the cilium, whose course may be followed through the depth of the section. While the tubules form a disorderly knot in the centre of the outer segment, several radiate outwards to the plasma membrane between the two lamellae.

The next stage of development was marked by the formation of lamellae at the base of the outer segment, as shown by their continuity with the plasma membrane (Figs. 9, 10). These sites of lamella formation were observed regularly, as is indicated by their presence in two neighbouring outer segments in Figure 10. The height of the stacks of horizontal lamellae increased progressively with age, from a maximum of 1–2 μm at 0 days (Fig. 10), to 6 μm at 13 days (Figs. 11, 12) and 18 μm at 35 days (Fig. 13). This was attributed to the addition of new lamellae at the base of the outer segment (Figs. 9, 10, 14), as has been demonstrated for the mature retina (Young, 1976). This increase in growth led to the displacement of the vertical lamellae further and further from the base of the outer segment (Figs. 9, 10, 11) until they eventually disappeared (Figs. 12, 13). Another consequence was that the cluster of tubules in the centre of the outer segment (Figs. 4, 5) was gradually displaced outwards away from the cilium by the horizontal lamellae (Fig. 10). Clusters of tubules were never observed in more mature outer segments; only the microtubules from the cilium located alongside the horizontal lamellae were present (Fig. 15). The fate of the vertical lamellae appeared to involve ingestion by the pigment epithelium. Phagosomes containing groups of lamellae of different orientations were first observed in the pigment epithelium at 9 days and more frequently at 13 days (Fig. 11). This was paralleled by the gradual disappearance of vertical lamellae from the outer segments. They predominated during the first and second postnatal weeks (Figs. 4–10). By 13 days, outer segments without vertical lamellae were in the majority (Fig. 12), while vertical lamellae were scarce at 18 and 23 days

Fig. 6. Transverse section through an outer segment containing the microtubules of the cilium (arrowheads) and several lamellae continuous with the plasma membrane (arrows). 3 day kitten central retina. 4% glutaraldehyde. Calibration, 0·5 μm.

Figs. 7–8. Stereopair of 0·5 μm sections, at 10° tilt, of radial section through an outer segment containing vertical lamellae (*v*) and a deep infolding of the plasma membrane (arrow). Newborn kitten area centralis. 1% glutaraldehyde.

Fig. 9. Radial section of outer segment with vertical lamellae (*v*) in its outer portion and horizontal lamellae (*h*) at its base, which are continuous with the plasma membrane (arrow). Newborn kitten area centralis. 1% glutaraldehyde.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and absent at 35 days (Fig. 13). Thus the removal of lamellae by the pigment epithelium commenced when the outer segments were still only one third of their full length (Fig. 11).

The actual means by which lamellae were formed in developing kitten retina outer segments, i.e. whether by invagination or evagination (see Introduction), was not determined. Profiles like those in Figures 4 and 5 are compatible with invagination of the plasma membrane because the spherical profile was not disturbed. In contrast, Figures 7 and 8 are compatible with either invagination or evagination of the plasma membrane depending on whether new membrane was added to the inner (vitread) face of the indentation or via the outer surface to the outer (sclerad) face, respectively. Once vertical lamellae were formed, however, they sometimes grew to great lengths, as is indicated by their presence alongside the main stack of horizontal lamellae; these were very common (Fig. 11). At the base of the outer segment, lamella formation was compatible with evagination of the plasma membrane (Steinberg *et al.* 1980) since the lamellae, which were of different lengths according to the stage of development, were always lined up with the cilium (Fig. 14). A new feature is shown in Figure 15. Quite often lamellae of vertical orientation were formed at the base of the outer segment, to be followed, presumably, by reorientation to the horizontal position. Some lamellae were either folded double or near double. In the former case, both rims were lined up against the cilium as if by positive attraction between the two. This attraction may also be inferred from less mature outer segments in which part of the rim of the lamellae appeared to be anchored to the microtubules of the cilium (Fig. 9). This will be discussed later.

The development of cone outer segments was followed only incompletely due to the difficulty of making positive identifications. Immature cone outer segments were generally relatively large and contained several stacks of parallel lamellae. More mature cone outer segments had a single stack of horizontal lamellae (e.g. Fig. 5, Morrison, 1982) which were observed to be continuous with the plasma membrane, exactly as in Figure 14. The only conclusion to be drawn about their development was that no striking difference from rod outer segment development was observed.

Outer segments preserved by the three methods of fixation had similar appearances, in that they all contained vertical lamellae and sometimes contained tubules (e.g. Figs. 6, 9, 10). Thus the possibility that these may have been due to a specific fixation method may be excluded. The possibility of artefacts arising from the delay in transferring the retina to fixative (which amounted to 1–2 minutes) may also be excluded. The second retina which was removed from the kitten was always as well fixed as the first, despite the additional time delay. Even if fixation was delayed for 15 minutes, as in an adult rat retina, the lamellae were still perfectly intact. Serious distortions did arise, however, when the retina became detached from the pigment epithelium. In addition to a scalloped, irregular outline, the outer segments contained

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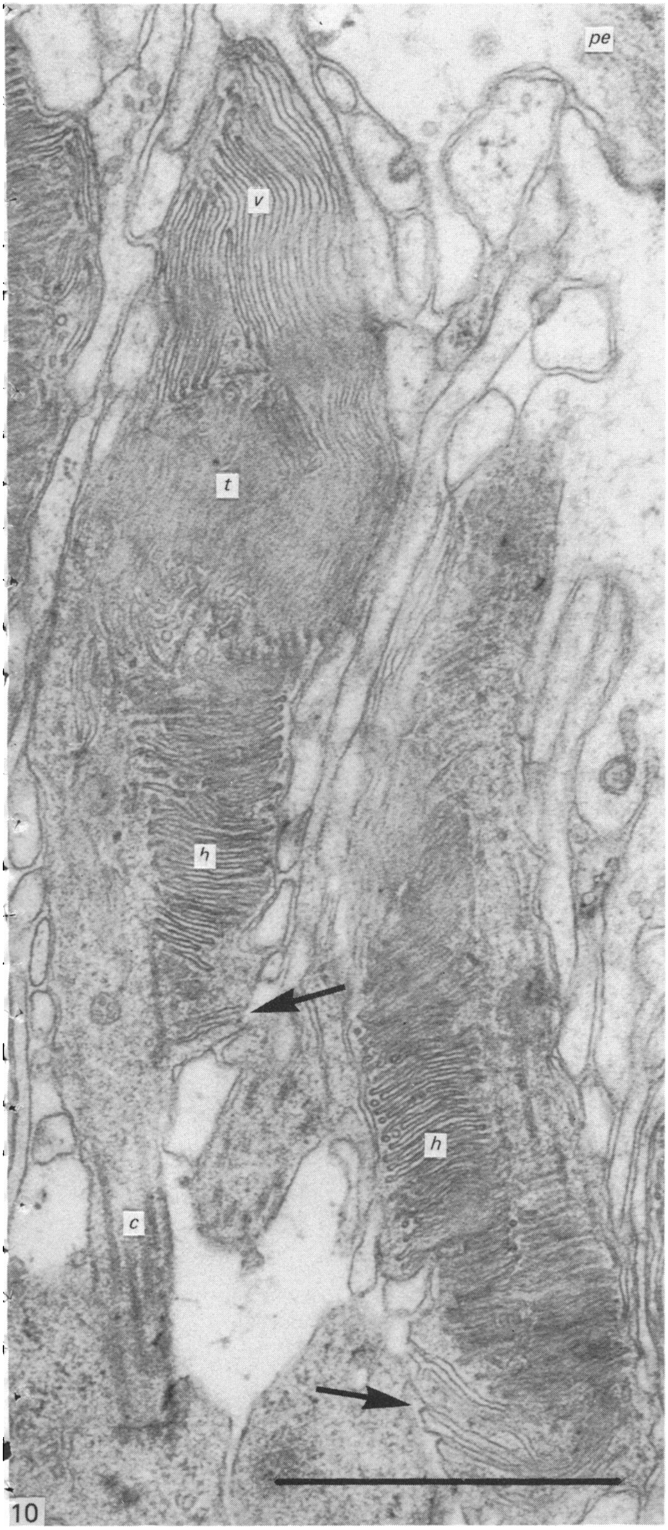
Fig. 10. Two outer segments with horizontal lamellae (*h*), some of which are continuous with the plasma membrane (arrows). One outer segment (left) contains vertical lamellae (*v*) in its outer part and tubules (*t*) at its centre. Newborn kitten area centralis. 1 % OsO_4.

Fig. 11. Two outer segments with long stacks of horizontal lamellae (*h*). At right, vertical lamellae (*v*) are present in outer part of outer segment. Some are also present, in both outer segments, alongside the main stack of horizontal lamellae. At top, discarded portion of an outer segment (*d*) has been ingested by pigment epithelium (*pe*). 13 day kitten central retina. 4 % glutaraldehyde.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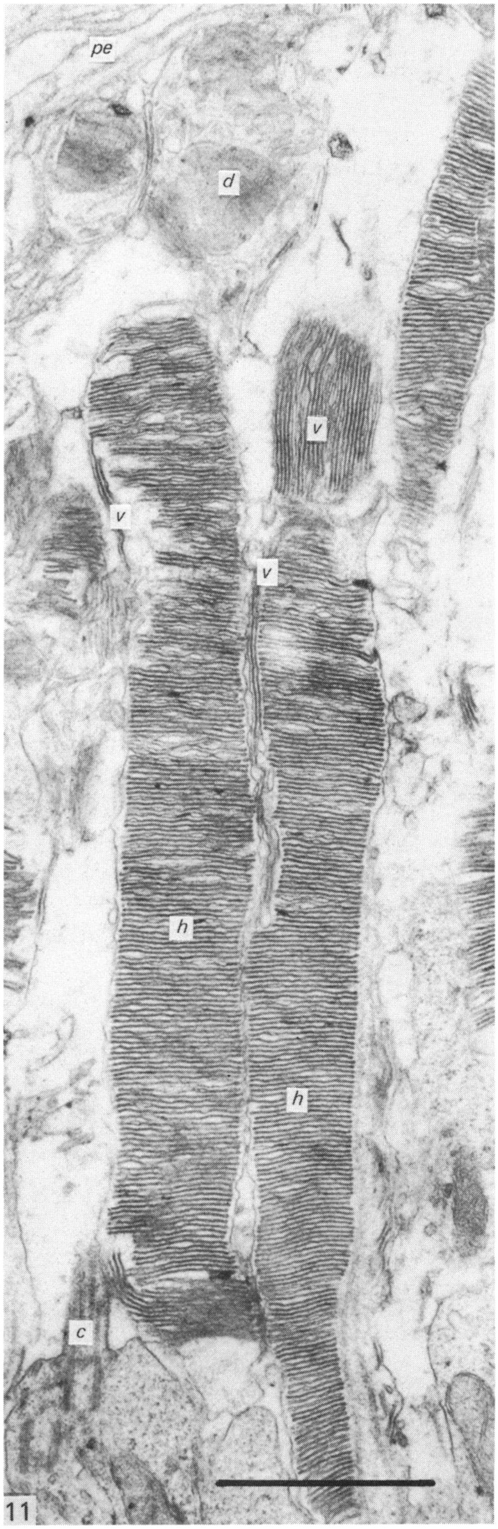
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large vacuoles that were not normally observed. The scalloped outline (which probably represented the imprints of processes of pigment epithelium) could have been thought to resemble invaginations were it not for its presence over the entire surface of the outer segment, irrespective of its size. Therefore it was believed that the detached outer segments were abnormal compared with intact retinae, and they were discounted in the analysis of outer segment morphogenesis.

DISCUSSION

From the present study of developing kitten rod outer segments, the following scheme is proposed for their sequence of development (Fig. 16). A balloon-shaped outer segment arises by expansion of the end of the cilium, presumably by addition of membrane and cytoplasm synthesised in the inner segment (Young, 1976). It is proposed that the microtubules which are present in the outer segment at this time may support the outer segment as part of its cytoskeleton, as originally suggested by Shaw Dunn (1975) in developing human photoreceptors. Lamellae are proposed to form in the outer segment when the surface area increases at a disproportionately faster rate than the cytoplasm. This process has been shown in the present study to be capable of occurring anywhere over the surface of the outer segment. In this respect, it provides evidence supporting the suggestion of McArdle *et al.* (1977) that the lamellae are formed at the outer surface of the outer segment. The present study also avoids problems of interpretation in that all the retinae studied had the pigment epithelium attached. In contrast, McArdle *et al.* and the majority of early workers show illustrations of detached outer segments which contained, it is believed, artefactual distortions. When lamellae are formed, it is proposed that their opposing faces are naturally drawn together by long range forces of attraction (London–Van der Waals forces) as described by Curtis (1967). The action of these forces is also proposed to cause lamellae to assemble naturally into stacks with regular intervals between lamellae. Once the young outer segment becomes filled with lamellae, a new site of lamella formation at the base of the outer segment arises. This stage is probably what was observed by Sjostrand (1959) and Vogel (1978*a*) when they concluded that immature outer segments formed lamellae at this location. Some evidence of attraction between the rims of the lamellae, which consist of globular proteins not present elsewhere in the lamella (Sjostrand & Kreman, 1978), and the microtubules of the cilium was presented in the present study. In the restricted volume at the base of a mature or relatively mature outer segment, this would have the effect of drawing the lamellae into a horizontal orientation. In immature outer segments where the microtubules penetrate only incompletely into the outer segment (which has a relatively

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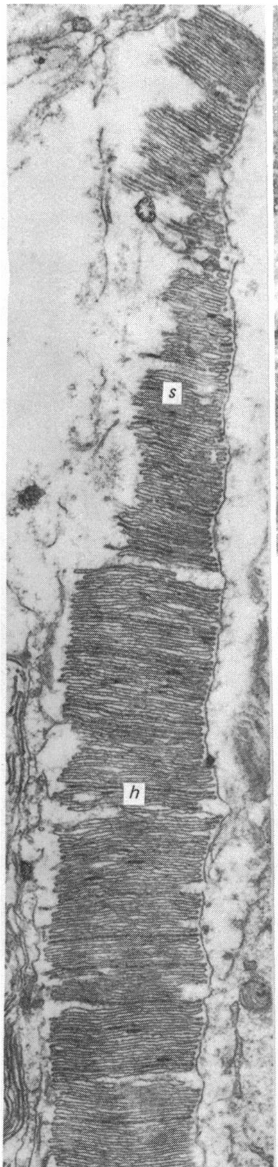
Fig. 12. Long outer segment containing horizontal lamellae only (*h*) though short lamellae (*s*) are present in its outer part. 13 day kitten central retina. 4% glutaraldehyde.

Fig. 13. Entire mature rod outer segment (*os*) from 35 day kitten central retina showing horizontal lamellae only. 1% glutaraldehyde.

Fig. 14. Enlargement of base of outer segment in Fig. 12 (×2) showing horizontal lamellae continuous with the plasma membrane (arrows).

Fig. 15. Two outer segments with bases containing lamellae in non-horizontal orientations. Vertical lamellae in the process of formation are indicated by arrows. Lamellae folded double, with edges lined up against the microtubules of the cilium, are indicated by arrowheads. 13 day kitten central retina. 4% glutaraldehyde.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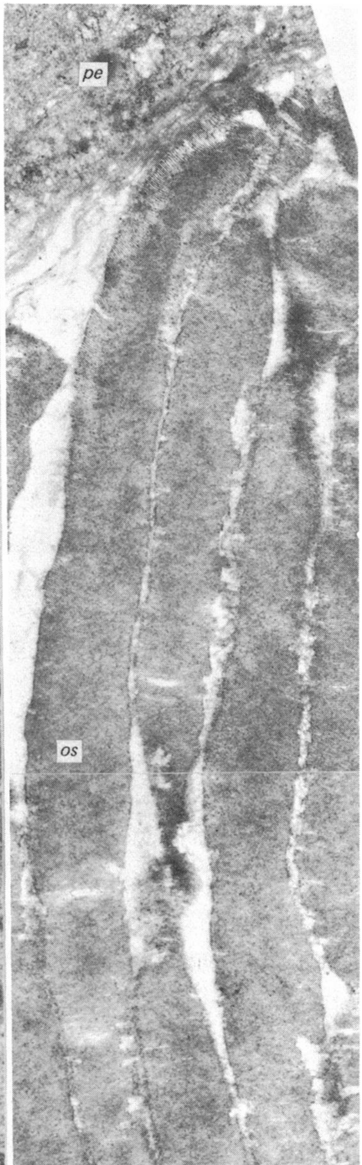
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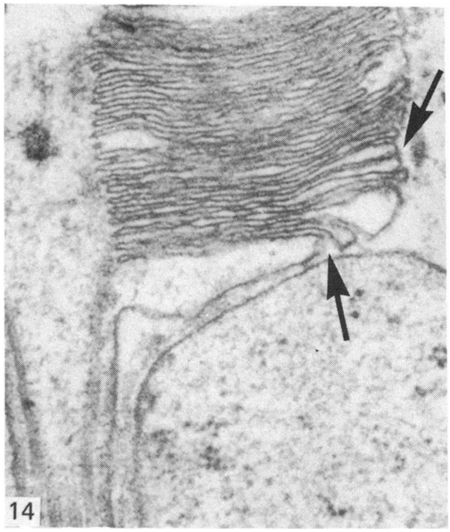
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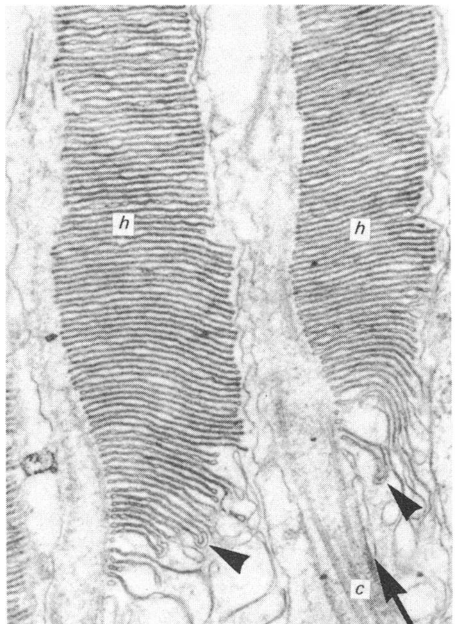
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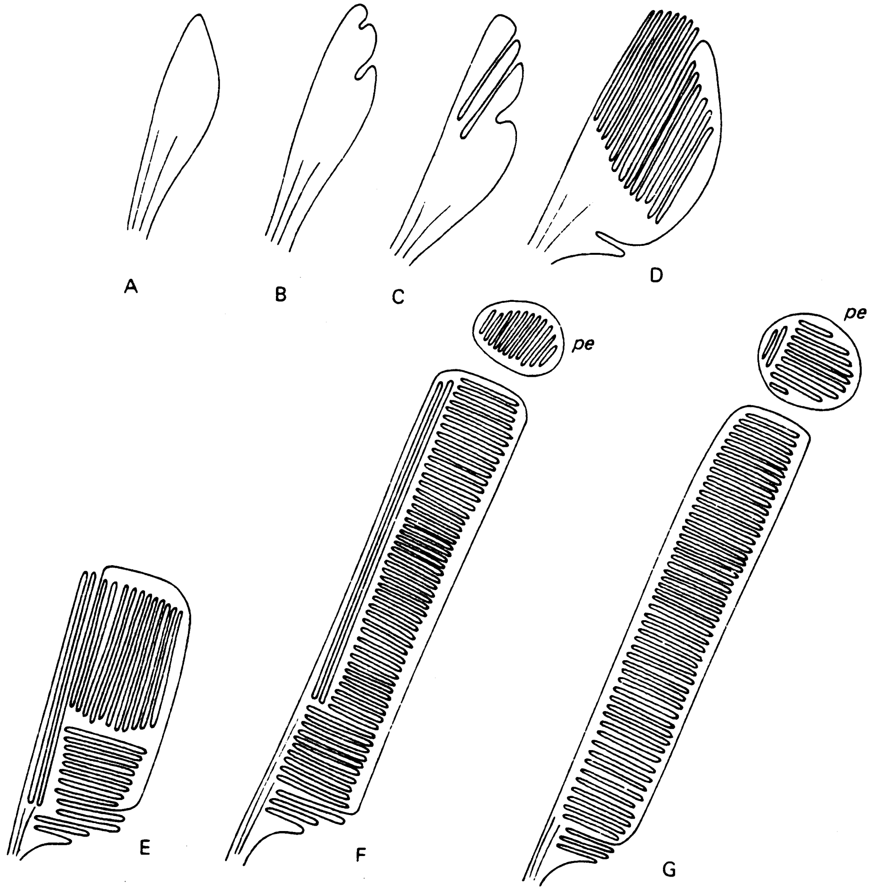

Fig. 16 (A–G). Scheme for the morphogenesis of kitten rod outer segments based upon the micrographs presented in Figs. 1–15. (A) Rudimentary outer segment. (B) Indentations of plasma membrane. (C) Formation of vertical lamellae. (D) Commencement of formation of horizontal lamellae. (E) Co-existence of vertical and horizontal lamellae. (F) Commencement of removal of vertical lamellae by pigment epithelium (*pe*). (G) Outer segment with horizontal lamellae only.

large volume, in which the lamellae may drift about) no such constraint on the orientation of the lamellae is present. The continuous addition of lamellae at the base of the outer segment leads to a stack of ever increasing height which displaces the vertical lamellae further outwards. Eventually, it was observed that the vertical lamellae were ingested by the pigment epithelium, which was shown by LaVail (1973) to be part of the normal function of these cells. The importance of this removal of vertical lamellae was shown in the dystrophic rat, in which the failure of the pigment epithelium to ingest lamellae leads to the formation of vast whorls of lamellae resulting, eventually, in retinal degeneration (Dowling & Sidman, 1962).

The scheme presented in Figure 16 provides an explanation for the occurrence of vertical lamellae described in this study and by numerous other investigators (see Introduction). It explains their removal by the pigment epithelium to leave an outer segment of mature appearance. It also offers an explanation for the prominent occurrence of tubules prior to lamella formation (Tokuyasu & Yamada, 1959, 1960; Ueno, 1960, 1961; Yamada & Ishikawa, 1965; Shaw Dunn, 1975; Spira, 1975). It also provides an explanation for the occurrence of immature outer segments which contained horizontal lamellae only, which were sometimes observed (Fig. 3, Morrison, 1982). Because the first lamellae are proposed to arise at any location over the surface of the outer segment, sometimes they must be orientated horizontally, thus giving rise to an outer segment with horizontal lamellae only. It is also no longer necessary to postulate the formation of lamellae from the collapse of smooth reticulum (Weidman & Kuwabara, 1968; Greiner & Weidman, 1978) which in any case was based on insubstantial evidence.

No firm conclusion was drawn about whether lamellae were formed by invagination (Nilsson, 1964) or evagination (Steinberg *et al.* 1980). In the first instance, it is doubtful if it is an 'either–or' situation. The micrographs presented by Nilsson are eminently compatible with an invagination hypothesis, while Steinberg and colleagues' results, and their demonstration of the sequence of rim formation in the lamellae, constitute very firm support for an evagination mechanism. In fact, the two theories may not be all that different. An important factor may be the amount of cytoplasm at the base of the outer segment. New membrane coming from the cilium must flow outwards away from the cilium. If there is ample cytoplasm at the base of the outer segment, new lamellae may be formed from the plasma membrane inwards towards the cilium, i.e. by invagination, as in Nilsson's micrographs. Should the amount of cytoplasm be limited, the lamellae may be formed simultaneously as new membrane flows outwards from the cilium, i.e. by evagination, as in Steinberg and colleagues' micrographs and Figure 14. In this way it would be possible for a developing outer segment to form lamellae by invagination or evagination depending upon the volume of the outer segment and the rate of membrane synthesis. It is conceivable that rim formation could occur in the manner described by Steinberg *et al.* in either process.

It is the presence of vertical lamellae, however, which marks a major difference between mammals which have them (present Results and Introduction) and amphibia which do not (Nilsson, 1964; Kinney & Fisher, 1978). This may be a genetic difference, because amphibians form an L-shaped outer segment which gives rise to horizontal lamellae (Kinney & Fisher, 1978) while mammalian outer segments always appear to be balloon-shaped. Alternatively, differences in the rate of growth may account for the differences. Mammalian outer segments attain a considerable volume before lamella formation commences, which would allow the lamellae to be located at different orientations. Amphibian outer segments seem to have a smaller volume, thus constraining the lamellae to the horizontal orientation. At first sight, it would appear that by producing vertical lamellae, mammalian photoreceptors were wasting membrane synthesis. However, there is nothing uncommon in this because a property of certain epithelia, e.g. in the alimentary canal, is to produce vast amounts of membrane (Young, 1976).

SUMMARY

The sequence of photoreceptor outer segment morphogenesis has been studied in the developing kitten retina by the examination of serial ultrathin sections and stereopairs of semithin sections. After the outer segment arose as an expansion of the outer end of the cilium, lamellae which had vertical or near-vertical orientations were formed over the whole surface of the outer segment. Subsequently, lamellae of horizontal orientation were formed at the base of the outer segment. The latter

gave rise to a stack of horizontal lamellae which increased in height, so displacing the vertical lamellae further and further from the base of the outer segment. These vertical lamellae were eventually ingested by the pigment epithelium, resulting in outer segments which contained horizontal lamellae only.

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